In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 11-693V

(to be published)

OLIVIA BENDER,	*	
	*	
	*	Filed: July 2, 2018
Petitioner,	*	
	*	Transverse Myelitis ("TM");
v.	*	Meningococcal Vaccine;
	*	Hepatitis A ("Hep A") Vaccine;
SECRETARY OF HEALTH AND	*	Medically Acceptable Timeframe;
HUMAN SERVICES,	*	Althen Prong Three; Biologic Mechanism; Reliability of Expert
	*	Testimony
Respondent.	*	
	*	

Bruce William Slane, Law Office of Bruce W. Slane, P.C., White Plains, NY, for Petitioner.

Lara Englund, U.S. Dep't of Justice, Washington, DC, for Respondent.

DECISION ON REMAND DENYING ENTITLEMENT[1]

On October 19, 2011, Olivia Bender filed this action seeking compensation under the National Vaccine Injury Compensation Program (the "Vaccine Program"[2]). Petition ("Pet.") (ECF No. 1). Petitioner alleges that she developed transverse myelitis ("TM") as a result of the meningococcal and Hepatitis A ("Hep A") vaccines she received on May 29, 2009. Pet. at 1.

[1] This Decision will be posted on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Decision will be available to anyone with access to the internet**. As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the published ruling's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen (14) days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the entire Decision will be available in its current form. *Id.*

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (codified as amended at 42 U.S.C. § 300aa-10 through 34 (2012)) (hereinafter "Vaccine Act" or "the Act"). All subsequent references to sections of the Vaccine Act shall be to the pertinent subparagraph of 42 U.S.C. § 300aa.

An entitlement hearing was held in Washington, DC, on February 9-10, 2017, and on October 6, 2017, I issued a decision denying entitlement. Petitioner subsequently filed a timely motion for review on November 3, 2017, and the Court of Federal Claims granted the motion, remanding the matter to me to reevaluate the testimony of Petitioner's primary causation expert, Dr. Vera Byers, and include a corrected analysis in a new discussion of the causation test set by the Federal Circuit in *Althen v. Secretary of Health & Human Services*, 418 F.3d 1274, 1278 (Fed. Cir. 2005). *See Bender v. Sec'y of Health & Human Servs.*, 2018 WL 2347163 (Fed. Cl. May 23, 2018) ("Remand Order").

I have now re-reviewed all expert reports filed in this case, the trial testimony, the medical record, and the numerous items of medical and scientific literature filed by both sides. For the reasons stated in below, I hereby DENY entitlement. Even after re-evaluating the record, and accounting for my prior error regarding Dr. Byers's opinion on the biologic mechanisms relevant to her causation theory, I still find that Petitioner has failed to carry her burden of proof. Her causation theory fails to link the relevant vaccines to TM with reliable evidence, relies on biologic mechanisms that have not been shown to occur in the absence of some other instigating factor, and is undercut by reliable epidemiologic evidence pertaining to the vaccines in question. Her experts were also generally unpersuasive in setting forth her causation theory. Moreover, even if her causation theory had been established in accordance with the applicable legal standards, Petitioner's claim would still falter on the remaining two *Althen* prongs. In particular, the timeframe in which her TM began remains too long after vaccination to be medically acceptable as causal, and there is insufficient preponderant evidence to conclude that in this case that these two vaccines "did cause" Petitioner's TM.

I. Factual Background

Receipt of Vaccines and Subsequent TM Onset

On May 29, 2009, Olivia Bender received the Hep A and meningococcal (marketed as "Menactra") vaccines after a physical examination. She was fourteen years old and had no prior health problems. Ex. 8 at 4, 6. There is no record evidence of any reaction to either of these vaccines in the intervening period before the incident that caused Ms. Bender to seek medical treatment, and neither Petitioner nor the other fact witnesses testifying in this action have offered testimony suggesting that any symptoms were occurring during this period despite the absence of corroborative proof.

While on a trip with other teenagers to the western half of the United States, on July 10, 2009 (42 days after vaccination), Ms. Bender began to experience back pain while riding on a

passenger bus. Ex. 15 at 79.[3] An hour or so later, upon disembarking from the bus, Ms. Bender experienced a sudden loss of sensation in her legs, causing her to collapse onto the pavement into a sitting posture. Ex. 1 at 2; Ex. 15 at 79. She was immediately taken to the nearest hospital - Kingman Regional Medical Center ("KRMC") in Kingman, Arizona, where a variety of tests and lab work was performed, including CT scans of Petitioner's spine (cervical, thoracic, and lumbar regions); a urinalysis; and a complete blood count ("CBC"). Ex. 1 at 4-8.

Efforts to Identify Source and Nature of Petitioner's Illness

On examination, Petitioner had no sensation below her umbilicus and no reflexes in her lower extremities. Ex. 1 at 2-5. The results of the evaluation were otherwise largely unremarkable, except CT scans of the thoracic, cervical, and lumbar spine showed mild spinal stenosis, mild scoliosis, and mild disc bulging. *Id.* at 6-11, 25-28. The CBC showed leukocytosis.[4] *Id.* at 6. There was no evidence of nerve damage, but the immediate treater's impression was that the Petitioner was experiencing a spinal cord compression. *Id.* at 13.

To obtain specialized treatment and diagnosis (since KRMC did not have the medical equipment required to perform an MRI), Ms. Bender had to be transferred to Sunrise Hospital in Las Vegas, Nevada ("Sunrise") for a neurologic consult. *See generally* Ex. 15; Tr. at 14. Treaters performed MRIs on July 10 and 14, 2009. Ex. 15 at 80, 139-40, 146-53. The July 10th MRIs were performed on the cervical, thoracic, and lumbar spine regions[5], plus the brain, with and without contrast[6], with the results of the cervical, lumbar, and brain MRIs deemed normal. *Id.* at 146-53.

[3] Certain medical records could be read to suggest that some of Petitioner's symptoms may have begun even sooner, in the 24-hour period before she first sought medical care. Specifically, some records indicate that Petitioner informed initial treaters that she had experienced mild lower back discomfort after "go-kart riding" the day before her fall, and that she noticed back pain again the next day prior to disembarking from the tour bus. Ex. 15 at 86. At hearing, however, Ms. Bender testified that she had merely been a passenger in a bumpy jeep ride over rough terrain, and that she had experienced some subsequent back pain due to the rough ride but that it had not persisted. Transcript ("Tr.") at 10-11. I cannot from the medical records ascertain if the back pain is attributable to any prior activities involving Petitioner – although the medical record does corroborate that Petitioner experienced *some* kind of back pain before her collapse incident.

[4] Leukocytosis is defined as the transient increase in the number of leukocytes/white blood cells in the blood, and can occur after strenuous exercise, or pathologically accompanying hemorrhage, fever, infection, or inflammation. *Dorland's Illustrated Medical Dictionary* 1028 (32nd ed. 2012) (hereinafter "*Dorland's*").

[5] The thoracic spine connects with the cervical spine above and the lumbar spine below, running from the base of the neck down to the abdomen. It is the only spinal region attached to the rib cage. The cervical spine is the part of the spine attached at the base of the skull comprising of the neck, while the lumbar spine is the part of the spine below the thoracic spine pertaining to the lower back between the thorax and pelvis. *Dorland's* at 1749.

[6] MRIs can be performed with injection into the blood of a contrasting agent, such as gadolinium, which serves to increase (or "enhance") the signal of certain types of lesions visible to the radiologist performing the imaging. Active or newer lesions are more likely to enhance than preexisting or older lesions, because the contrasting agent is able to enter the brain via an existing breach in the blood-brain barrier; once that barrier is repaired, and the contrast cannot

The results of the thoracic spine MRI, however, showed an abnormal T2 signal at the T11-12 levels (i.e. at the lower end of the thoracic region, closer to the lumbar spinal region), and "enhancement within the remainder of the cord," suggesting to the radiologist performing the MRI the presence of an "acute transverse myelitis." *Id.* at 146.

A second round of MRIs of the thoracic and lumbar regions of the spine was performed four days later, on July 14th, again with and without contrast - and the differences detected underscore the rapidly progressive character of the disease process Petitioner was then experiencing. Ex. 15 at 139-40. Now, the MRI of the thoracic region revealed an abnormal signal between the T8 and T12 levels – hence higher up than before - with increased T2 signals, and some enhancement of the distal, or lower, portions of the thoracic cord was detected. *Id.* at 139. The radiologist performing this MRI deemed the results "compatible with clinical history of transverse myelitis." *Id.* That same radiologist, however, was less equivocal in his reading of the lumbar MRI, noting "[s]ignal through the distal spinal cord is *abnormally increased* on the T2 and STIR sequences," and interpreting this result as more direct evidence of TM on its own.[7] *Id.* at 140 (emphasis added). The impression of Petitioner's treaters, given her "acute loss of neurologic function," coupled with a lack of evidence of any other obvious spine pathology and the location of lesions, was TM. *Id.* at 88.

Other testing performed on Ms. Bender was somewhat inconclusive. One such result from the CBC measured the segmental neutrophils ("SEGS"), finding them to be slightly high - usually an indication of stress or pain. Tr. at 173.[8] Serology for *Mycoplasma pneumoniae* IgM and IgG antibodies[9] were reported as positive, but PCR[10] testing for *Mycoplasma* DNA was negative. Ex. 15 at 122, 127, 133. However, an aspect of that lab report was later discovered by Petitioner to be in error - Petitioner's mycoplasma IgM titers were in fact negative, but had been incorrectly

reach the brain, lesions do not appear enhanced. *See W.C. v. Sec'y of Health & Human Servs.,* 100 Fed. Cl. 440, 444 (2011).

[7] STIR is an acronym for Short-TI Inversion Recovery (sometimes also called Short Tau Inversion Recovery), a type of MRI which uses an inversion recovery pulse sequence with specific timing so as to suppress the signal from fat. STIR, http://www.revisemri.com/questions/pulse_sequences/stir (last visited June 25, 2018).

[8] Dr. Chen commented on this CBC SEGS test result, noting that it could also point towards a preexisting bacterial infection, but could not in his view be relied upon as evidence of an existing viral illness absent other abnormal test results. Tr. at 174-75.

[9] Mycoplasma pneumoniae is a genus of bacteria that causes subclinical infections or mild respiratory tract disease. *Dorland's* at 1217. The presence of IgM antibodies suggests a recent infection, while IgG antibodies indicate a prior infection that may have been resolved for years. Tr. at 56.

[10] PCR stands for polymerase chain reaction, which is a "type of rapid nucleic acid amplification of specific DNA or RNA sequences, allowing small quantities of short sequences to be analyzed without cloning." *Dorland's* at 1601.

flagged by the lab report as positive. *Id.*, Tr. at 56.[11] Ms. Bender's doctors nevertheless appear to have initially relied upon the false IgM reading, diagnosing her with TM secondary to a mycoplasma infection and treating her with azithromycin.[12] *Id*. at 60-61, 80. The doctors at Sunrise seem also to have been including in their initial differential diagnosis an autoimmune etiology, requesting that Ms. Bender receive a neurology referral to help evaluate this possibility. *Id*. at 60. Importantly, however, initial treaters were also aware Petitioner had received the Menactra vaccine (*see*, e.g., Ex. 15 at 79, 89) – but none suggested or opined that it was causal of her illness.

At Sunrise, Petitioner underwent treatment with IVIG[13] and steroids but showed no improvement in her condition. On July 20, 2009, Ms. Bender was transferred for rehabilitation. The transfer diagnosis was "transverse myelitis secondary to mycoplasma infection." *Id.* at 15. Thereafter she received treatment at a facility closer to her home - Blythedale Children's Hospital in Valhalla, New York - remaining there through early September. Her diagnosis of TM secondary to mycoplasma infection was affirmed (without recognition of the error in the mycoplasma testing discovered by Petitioner). *See generally* Ex. 11. Ms. Bender was discharged from Blythedale on September 4, 2009, after learning how to manage her own care.

Subsequent Treatment

In the months thereafter in 2009, Petitioner received additional treatment that was partially aimed at identifying the etiology of her TM. First, she saw Dr. Oya Tugal, a pediatric hematologist, to evaluate if there might be a vascular explanation for her symptoms. *See* Ex. 14 at 3- 4. In the course of evaluating that question, Dr. Tugal requested additional MRIs of Ms. Bender's thoracic and lumbar spines, with and without contrast, and the MRIs were performed on November 6, 2009. *Id.* at 5-6. These new MRIs showed T2 signal intensity changes in the lumbar spinal cord from the T5 to T8-9 locations, but no abnormal enhancement (thus indicating no new lesions had developed). *Id.* at 5. Taking into account other testing intended to evaluate the vascular hypothesis, Dr. Tugal concluded that the overall results were consistent with the prior TM diagnosis but did not demonstrate thrombus, as has been suspected. *Id.* at 3.

Second, in December 2009, Ms. Bender saw Douglas Kerr, M.D., a neurologist at Johns Hopkins University with recognized expertise in diagnosing and treating TM, for a consultation.

[11] Ms. Bender's IgG titers were, however, correctly read as positive for a prior mycoplasma infection sometime in her childhood, although the precise timing of the prior infection cannot be identified. Tr. at 69.

[12] Azithromycin is used to treat bacterial infections. *Dorland's* at 187. Here, it was used to treat the mycoplasma pneumoniae infection that it originally seemed Ms. Bender had at the time.

[13] IVIG is a treatment for immunodeficiency disorders made of immune globulin and administered through the veins. *Dorland's* at 785.

Ex. 13 at 1-3.[14] Based on her "very rapid onset," Dr. Kerr theorized that the cause of Petitioner's condition might be a fibrocartilaginous embolism rather than TM, but he noted that the management of her condition would be the same, whatever the cause. *Id.* at 2. In the course of evaluating Petitioner, Dr. Kerr requested the opportunity to review her prior MRIs, in order to test his hypothesis. *Id.* at 2. A Johns Hopkins radiologist performed that review in April 2010, and determined that the signal alterations from the initial July 10, 2009 MRI of the thoracic and lumbar spine still suggested an "unknown etiology," other than a possible "ischemic/vascular injury." *Id.* at 4. It does not appear that Dr. Kerr performed any additional examinations of Petitioner thereafter, and the records from this visit with Dr. Kerr do not mention the vaccines received prior to onset of Ms. Bender's condition or propose that they were causal of her TM; they also do not repeat the earlier, mistaken assumption that her TM was secondary to a mycoplasma infection.

Dr. Kerr referred Petitioner to the Kennedy Krieger Institute's spinal cord injury center in Baltimore, Maryland, for therapy. Ex. 13 at 2. There, Petitioner has received treatment from Glendaliz Bosques, M.D. Ex. 7 at 127-34, 25-31; *see also* Ex. 18. On August 6, 2010, Dr. Bosques stated that petitioner was diagnosed with a T8 ASIA A spinal cord injury (meaning that she has no motor or sensory function below the T8 vertebra). Ex. 7 at 29, Ex. 11 at 115-16. No subsequent treaters have associated her TM with the vaccinations she received seven weeks before her immediate and first alarming symptoms.

II. Fact Witnesses and Expert Opinions

Petitioner presented three fact witnesses at hearing as well as two experts. Respondent also offered two experts.

A. *Fact Witnesses*

Three fact witnesses - Petitioner and her parents, Drew and Diane Bender – testified at hearing, addressing Petitioner's current condition as well as the circumstances of her initial TM presentation in 2009. Tr. at 5-29. They each offered short testimony regarding their recollection that Olivia had no prior health conditions before her TM diagnosis—including no symptoms of an infection, consistent with her negative IgM results. Tr. at 7-8, 19-20, 25-26. They also testified

[14] In addition to being one of Ms. Bender's treaters, Dr. Kerr was a co-author of an item of medical literature submitted by Petitioner. J. Graber, et al., *Interleukin-17 in Transverse Myelitis and Multiple Sclerosis*, J Neuroimmunology, 196:124-32 (2008), filed as Ex. 30, Tab 8 (ECF No. 104). Dr. Kerr is recognized as having specialized expertise in the study of TM. https://www.the-asci.org/controllers/asci/AsciProfileController.php?pid=500563 (last visited September 18, 2017) (noting that "Dr. Kerr has established the Johns Hopkins Transverse Myelitis Center which is the only such center in the entire world"). Dr. Kerr has offered opinions on behalf of petitioners in other Vaccine Program cases. *See*, e.g., *Flores v. Sec'y of Health & Human Servs*., No. 10-489V, 2013 WL 5587390, at *6 (Fed. Cl. Spec. Mstr. Sept. 12, 2013), *mot. for review den'd*, 115 Fed. Cl. 157 (2014), *aff'd*, 586 Fed. App'x 588 (Fed. Cir. 2014).

that on her trip, Olivia had not performed any activities that could have caused her back trauma. Tr. 10-11.

Olivia Bender provided additional details about the first symptom that precipitated emergency treatment. That day, she was travelling with her group by bus to a new location, but when she began to get off the bus at a rest stop, she felt her legs were "all pins and needles and tingly." Tr. at 13. As she proceeded off the bus, she recalled the feeling getting worse so she abruptly sat down. It was at that time that she realized she had no sensation in her legs, as she could not feel the heat of the pavement through her clothes despite the temperature being over 100 degrees. *Id*. After attempts by one of the adult supervisors of the trip to get Ms. Bender to stand, she was carried back onto the bus to go to the hospital. *Id*. Her testimony about her subsequent treatment was otherwise consistent with the medical records previously discussed.

B. *Petitioner's Experts*

1. Dr. Vera Byers

The first of Petitioner's two experts, Vera Byers, M.D., provided an immunological opinion that the Menactra or the Hep A vaccines caused Ms. Bender's TM. Dr. Byers prepared two expert reports (although only one was submitted as an exhibit) and testified at hearing.[15] *See* Report, dated Oct. 3, 2016, filed as Ex. 30 ("Byers Rep."); Tr. 29-163.

Dr. Byers attended the University of California, Los Angeles for her bachelor's degree, her masters in protein chemistry, and her Ph.D. in immunology. Tr. at 30; Byers CV, filed as Ex. 31 (ECF No. 102), at 3. Before entering medical school, Dr. Byers completed two fellowships: one in protein chemistry at Abbott Labs in Chicago, Illinois, followed by a fellowship in clinical and tumor immunology at the University of California, San Francisco ("UCSF"). Byers CV at 4; Tr. at 30. She then attended medical school and completed a three-year residency at UCSF, before becoming a member of the faculty. Byers CV at 4. Dr. Byers is presently a medical toxicologist

[15] Dr. Byers's first report was filed long after the deadline to submit reports in this case had expired, and without my prior approval. I permitted the report into evidence despite its dilatory character, but informed the parties that I would allow Respondent the opportunity to file a responsive report. *See* Order, dated Oct. 13, 2016 (ECF. No. 105). In addition, due to the looming trial date, plus Petitioner's prior disregard for my orders regarding deadlines for the submission of evidence, I stated that I would not permit the filing of a second report from Dr. Byers; instead, Petitioner would be permitted to address the contents of any final expert report filed by Respondent during the hearing, and (if necessary) file a post-trial written brief in support of Dr. Byers's testimony. *Id*. Petitioner nevertheless commissioned a second expert report from Dr. Byers in violation of my order, referencing it at trial and repeatedly requesting that it be permitted into evidence. Tr. at 44, 65-66. In response (and consistent with my October order), I informed Petitioner that I would allow Dr. Byers to testify to the substance of the second report in rebuttal to Respondent's expert testimony, and that Petitioner could reference points from Dr. Byers's unauthorized second report in her post-hearing brief. Petitioner agreed to my proposed concession. *Id.* at 393-94. Petitioner did not subsequently attempt to file again Dr. Byers's second report, although she did file a post-trial brief and 14-page reply, and she did not argue on review that my determination on this issue was in error.

and consulting medical director at Immunology Inc. of Incline Village, Nevada, and has frequently served as an expert witness in lawsuits, including Vaccine Program cases. *Id.* at 1-2. She has throughout her career maintained several positions as an allergist and immunologist performing research and clinical trials in a variety of different areas. Byers CV at 6-7; Tr. at 34-41. She has had no clinical practice for 10 to 15 years, however, and derives the majority of her income today from her work as an expert witness. Tr. at 121, 123-24.[16]

Dr. Byers was careful to state that her opinion drew solely upon her expertise in immunologic matters. Tr. at 42-46. For all matters pertaining to TM itself, she relied on the expert reports of Dr. Chen and his interpretation of Ms. Bender's medical records – which, by her own admission, she never directly reviewed. Byers Rep. at 5; Tr. at 42-43.[17]

Dr. Byers opined that Ms. Bender's receipt of the Menactra and Hep A vaccines caused her TM.[18] She defined TM as largely an autoimmune condition characterized by demyelination of the spinal cord. Byers Rep. at 6. Such demyelination can have disparate causes: inflammation propagated by myelin-attacking autoantibodies, or any number of other existing immune cells attacking the myelin sheath. *Id*. In Dr. Byers's view, the primary engine of Petitioner's illness was the vaccines' promotion of pro-inflammatory cytokines—particularly IL-6,[19] which is released by T cells. Tr. at 43; Byers Rep. at 6. As many items of literature filed by Petitioner state, IL-6 has been measured in elevated levels of individuals who experience TM, and also been found to mediate spinal cord injury. Byers Rep. at 6; A. Kaplin, et al., *IL-6 Induces Regionally Selective Spinal Cord Injury in Patients with the Neuroinflammatory Disorder Transverse Myelitis*, J. Clinical Investigation, 115(10):2731-41 (2005), filed as Ex. 30, Tab 12 (ECF No. 104-1) ("Kaplin"); I. Campbell, et al., *Neurologic Disease Induced in Transgenic Mice by Cerebral Overexpression of Interleukin 6*, 90 Proc. Natl. Acad. Sci. USA 10061-65 (1993), filed as Ex. 30, Tab 5 (ECF No. 104-1). Here, Dr. Byers proposed that "autoreactive antigen specific T cells" were

[16] In her rebuttal testimony, Dr. Byers seemed to contradict this admission about her 15-year lapse in treating patients, asserting that "for 20 years, I've been seeing patients with autoimmune diseases in private practice . . . . Tr. at 373. From my review of her CV, however, it appears that all of her efforts in the past 20 years have been working on clinical trials for drugs or testifying as an expert (Byers CV at 6-7), suggesting that assertions about recent clinical treatment activity were in error.

[17] Dr. Byers's report does state, however, that she relies in part on Dr. Chen's proposal that certain vaccines, including the meningococcal vaccine, are associated with TM. Byers Rep. at 5.

[18] Dr. Byers never specifically opined if one or the other vaccine was in her view more likely to be causal, and did explicitly testify that either of the proposed biologic mechanisms could "work" regardless of which vaccine was at issue. Tr. at 60. She did, however, testify with specificity about the immune-stimulative effect of Menactra and its connection to her overall theory. *Id.* at 153-54.

[19] IL stands for interleukin, a generic term for a group of multifunctional cytokines that are produced by a variety of lymphoid and nonlymphoid cells and have effects at least partly within the lymphopoietic system. IL-6 is a lymphokine produced by antigen- or mitogen-activated T cells that serves as a differentiation factor for B cells, and also stimulates immunoglobulin production by B cells. *Dorland's* at 949.

produced outside the central nervous system ("CNS"), but then "homed in" to the CNS and caused production of different cytokines (both in the periphery and also in the CNS) sufficient to promote an inflammatory, demyelinating process leading to TM. Byers Rep. at 7; Tr. at 101.

Although (as noted below) Program claimants need not establish a particular biologic mechanism to prevail, Dr. Byers offered a great deal of testimony regarding the mechanism she believed could have caused the two vaccines in question to initiate a pathologic process leading to TM. Notably, she unequivocally agreed that molecular mimicry[20] - a mechanism very often relied upon in Program cases to explain a pathologic autoimmune process – between components of the relevant vaccines and self structures was not a plausible primary biologic mechanism at work herein. Tr. at 47-48. She did so based on the admission that she could not identify sufficient homology between antigens from components of the Hep A and meningococcal vaccines Ms. Bender received and self-protein structures, nor did she believe that a "superantigen" contained in either vaccine could have nonspecifically stimulated T cells. Byers Rep. at 7; Tr. at 47, 48.

But Dr. Byers disputed that autoimmunity can *only* be the result of cross-reactivity mediated by B cells and encouraged by "shared epitopes" (i.e. via molecular mimicry). Byers Rep. at 6. Instead, she maintained that "more recent studies" demonstrated that autoimmunity could be driven by cytokines, which can stimulate T and B cells[21] even if an initial cross-reaction due to an autoimmune attack has not occurred. *Id.* at 6. She thus proposed two alternative mechanisms that could have been involved in the pathogenesis of Ms. Bender's TM. Tr. at 47, 49.[22]

First, Dr. Byers discussed the concept of "bystander activation." Tr. at 49-50, 53-54, 59. Dr. Byers defined bystander activation (or what she also termed "polyclonal activation") to occur

[20] Molecular mimicry, Dr. Byers explained, "simply means that the 3D structure of the antigen that is presented on the surface of the macrophage generates an immune response which cross-reacts with some of the body's own components and therefore it triggers an autoimmune reaction." Tr. at 47.

[21] T cells and B cells are both types of lymphocytes – mononuclear, nonphagocytic leukocytes, found in the blood, lymph, and lymphoid tissues that are the body's immunologically competent cells and their precursors. They are divided on the basis of ontogeny and function into two classes, B and T lymphocytes, responsible for humoral and cellular immunity, respectively. *Dorland's* at 1084.

[22] Dr. Byers's testimony regarding the extent of her rejection of molecular mimicry as a plausible mechanism in this case was somewhat contradictory (although this may be attributable to nuances in the theory that she failed to articulate clearly in testifying). Thus, moments after affirmatively stating at trial that she was *not* opining that molecular mimicry was a reasonable mechanism to explain how Ms. Bender developed TM from receipt of the Hep A and meningococcal vaccines, she stated that "it's either [bystander activation], in which case – in which I think Dr. Lotze agrees with me, or alternatively, *it could be molecular mimicry*." Tr. at 50 (emphasis added). She later, however, explained (albeit confusingly) that she actually was referring to her alternative mechanism of epitope spreading, which she defined as "just molecular mimicry on a very individual basis" – meaning that individual susceptibility to a given antigen would result in a cross-reaction due to a foreign antigen mimicking a self structure specific only to that individual, and therefore not seen on a widespread basis in the population to the extent necessary to identify the exact homology at issue. *Id.* at 50-51, 52.

when "you have cytokines that are released by either an infection or a vaccination which not only activates [the] antigen-specific immune system, but also activates other reactive cells as well, so they . . . can go after their true target, which is actually autologous self-antigens." *Id.* at 53. These autoreactive cells (which include both T and B cells) are "laying around" the immune system but can (via certain immune processes) be activated, resulting in increased inflammation and eventually an autoimmune condition. *Id.* at 49, 59. She deemed bystander activation the "most probable" mechanistic explanation for how the Hep A or meningococcal vaccines produced Ms. Bender's TM. *Id.* at 100-01; Byers Rep. at 7.

To support bystander activation as a plausible mechanism, Dr. Byers relied heavily on the concept that vaccination would unleash a "cytokine storm." Tr. at 49, 54. Cytokines are proteins used by the immune system to communicate with other body tissues. *Id.* at 93. Innate immune system processes can (in reaction to vaccination) produce a number of different kinds of cytokines that promote inflammation – but some of which, like IL-6, can be damaging, either due to their propensity to encourage additional inflammation or simply on their own. *Id.* at 96, 98. She could not, however, identify any evidence that the mere injection of cytokines in the periphery could result in an autoimmune process attacking the central nervous system, or evidence that certain of the cytokines she highlighted, such as IL-6, had been shown to be directly harmful to the spinal cord (as opposed to simply being present in the CSF of individuals with TM), although she claimed familiarity with animal models that would support her contention. Tr. at 144, 146.[23]

As a basis for such assertions, Dr. Byers offered literature that she maintained suggested that inflammation caused by receipt of a vaccination can provoke an autoimmune response via bystander activation. Tr. at 49, 54; K. Murali-Krishna, et al., *Counting Antigen-Specific CD8 T Cells: A Reevaluation of Bystander Activation During Viral Infection*, Immunity, 177–87 (1998), filed as Exhibit 30, Tab 18 (ECF No. 104-1) ("Murali-Krishna"). Murali-Krishna was an animal study aimed at better understanding how wild viral infections (as opposed to vaccination, which the authors did not evaluate) result in the proliferation of a particular kind of lymphocyte "killer" cell (CD8 T cells) effective in the immune response to the infection. Murali-Krishna's authors noted that because "only a small fraction . . . of the activated CD8 T cells are antigen specific at the peak of primary response," bystander activation of those nonspecific cells had been proposed to explain their proliferation. Murali-Krishna at 177. The authors of this study attempted to measure the number of these nonspecific T cells responding to a lymphocytic choriomeningitis viral infection in mice – but found that "as many as 70 percent of the responding CD8 T cells . . . can be virus specific," and therefore there should be a "revision of our current models of viral-induced T cell proliferation that are based on the notion that most of the responding T cells are not

[23] At several times during her testimony, Dr. Byers referenced different studies that she said existed and which supported her points, including the argument that cytokines could be directly harmful. *See, e.g.*, Tr. at 51, 144, 147, 151-52. I informed Petitioner that I would accept any such literature referenced at hearing but filed thereafter. Tr. at 65. Petitioner never filed any such items post-hearing, however.

specific to the infecting virus." *Id.* at 183. Despite a finding seemingly at odds with her opinion, Dr. Byers asserted that Murali-Krishna supported her theory, since it at least found that *some* nonspecific T cells had been stimulated (30 percent). Tr. at 142-43.

Dr. Byers did not offer any medical literature directly involving the propensity of the Hep A and meningococcal vaccines to cause the kind of cytokine-driven, non-antigen-specific inflammatory response that she was proposing could become pathogenic via this mechanism. She also did not propose that this is a case in which adjuvants (contained in vaccines to increase their immune-stimulating effects) are provoking cytokine upregulation. Tr. at 88-89. She nevertheless maintained that because Menactra (the form of meningococcal vaccine at issue) contains a diphtheria toxoid component to increase its "immunogenicity," it inherently has the capacity to provoke a sufficiently strong immune response to have the effect theorized. *Id.* at 153-54, 383-84.[24]

There were other limitations to the invocation of bystander activation as a likely mechanism that Dr. Byers struggled to address. Dr. Byers cited no evidence that the process she proposed had occurred as theorized, relying simply on the absence of *other* contrary causation evidence. She also acknowledged there were tests that could measure cytokine levels (Tr. at 106), but could not identify what level was necessary to be pathologic (and in this case there are no tests that would directly or indirectly suggest that the Petitioner experienced such levels in the weeks before onset of her TM).

The other mechanism proposed by Dr. Byers as key to the process by which the Hep A or meningococcal vaccines could have initiated an autoimmune process resulting in TM was epitope spreading. She defined it as occurring "when the primary antigen [from a vaccine] that is being presented [to the immune system] does not have – cannot find its perfect specific T cells to wipe out, and so therefore more and more cells of less specificity are allowed into the – into the mix." Tr. at 52, 60-61 ("in the case of epitope spreading, those highly specific cells that could very rapidly eliminate the infection would not be there, primarily on a genetic basis"), 149-50. Dr. Byers characterized epitope spreading as a kind of "poor" molecular mimicry unique to these genetically-susceptible individuals, whereby the nonspecific immune response to a foreign antigen (which does not mimic a self structure or tissue) causes T cells highly reactive to *other* self structures to initiate an autoimmune reaction, in a molecular mimicry-like attack. *Id.* at 52 ("it's just molecular

[24] Menactra is a sterile solution of meningococcal polysaccharides conjugated to diphtheria toxoid. *Dorland's* at 2016. Respondent's immunologist expert, Dr. Forsthuber, agreed that the diphtheria toxoid was included in the vaccine to increase its immunogenicity (although he did not accept the broader point that the meningococcal vaccine can have the alleged pathogenic effect simply because it contains that toxoid). Forsthuber Rep. at 5. Dr. Byers also proposed that the fact that Ms. Bender likely received a diphtheria toxoid-containing vaccine in the past could have prompted her (via an immunologic memory response) to react to Menactra – although she points to no evidence that this occurred, and offered no scientific or medical support for her contention that the anamnestic response to this vaccine component could be pathologic in the way proposed. Tr. at 153-54.

mimicry on a very individual basis"), 53, 60-61, 151, 155. She represented that the reliability of epitope spreading as a pathologic mechanism was confirmed by animal studies. *Id.* at 86, 152; P.V. Lehmann, et al., *Spreading of T-Cell Autoimmunity to Cryptic Determinants of an Autoantigen*, 358 Nature 155-57 (July 1992), filed as Ex. 30, Tab 16 (ECF No. 104-1) ("Lehmann").

Dr. Byers went on to cite other evidence that she purported demonstrated an association between different vaccines and TM. Consistent with arguments made by Dr. Chen (as discussed below), she observed that the package insert included with the meningococcal vaccine received by Ms. Bender allowed for the possibility that TM could occur after receipt of the vaccine, and that this constituted some recognition by the vaccine manufacturer that the risk was real. Byers Rep. at 5; Tr. at 89-90. She referenced case study reports involving observed associations between vaccines and TM. *Id.* at 74, 76, 83; N. Agmon-Levin, et al., *Transverse Myelitis and Vaccines: A Multi-Analysis*, 18 Lupus 1198-1204 (2009), filed as Ex. 30, Tab 1 (ECF No. 104-1) ("Agmon-Levin"). Agmon-Levin does not address a single case study involving either of the vaccines relevant to this case, however. Agmon-Levin at 1200. And she relied heavily on reports from the Vaccine Adverse Events Reporting System (VAERS) detailing many instances in which a person receiving the Hep A or meningococcal vaccine reported developing TM thereafter. Byers Rep. at 5; Tr. at 74 (deeming VAERS data "really critical, *because it's all we've got*") (emphasis added), 80-81, 89-90, 127, 159 ("[t]he best data I have on that is the VAERS database and that's it").[25] On cross examination, however, she agreed that not all vaccines were equally as likely to cause TM, or any autoimmune condition – and she could not identify what would make one vaccine over another more or less likely to produce an autoimmune disease. *Id.* at 132-33, 137-38.

Besides defending the causal role Ms. Bender's vaccines could have played in developing her TM, Dr. Byers argued that the timeframe in which Ms. Bender experienced her first TM symptoms post-vaccination was medically appropriate, despite the fact (as she acknowledged) that Ms. Bender's medical records revealed "no symptoms of any kind of an inflammation until the sudden onset of day 41 or 42 of the [TM]." Tr. at 102. In support, she referred again to Agmon-Levin, which considered several instances of wide time intervals between onset of TM and a variety of vaccines. Tr. at 77. Agmon-Levin contained a chart based on case reports of 37 instances of post-vaccination TM, setting forth a wide variety of temporal periods between vaccination and onset. Agmon-Levin at 1200. Dr. Byers expressly reproduced the chart in her expert report and discussed it in her trial testimony, noting that for the cases discussed (none of which involved either of the vaccines in question), timing of onset ranged from four days to 27 weeks. Byers Rep. at 4; Tr. at 76-77. She acknowledged on cross examination, however, that many of the individual case studies relied upon in Agmon-Levin were inapt – for example, some of the case studies

[25] VAERS is a national vaccine safety surveillance program co-sponsored by the Centers for Disease Control and Prevention and the Food and Drug Administration, and allows individuals who believe they may have experienced a vaccine reaction to make a report of the incident. *See* https://vaers.hhs.gov/index (last visited August 16, 2017).

involved individuals whose TM could be attributable more to a preexisting condition or intervening disease factor than simply to vaccination. Tr. at 133, 134-36.

Based on Agmon-Levin as well as her own expertise, Dr. Byers proposed that four weeks, or 28 days, would typically be the longest period in which she would expect an immune process to result in TM. Byers Rep. at 7. Here, as Dr. Byers conceded, 42 days was "a little long," since she would have expected primary response to the meningococcal vaccine to occur within a month, or even as soon as two weeks. Tr. at 77, 79. She nevertheless maintained that it did not preclude that Ms. Bender's TM was vaccine-caused. *Id*. at 77. In so doing, she emphasized that she would not place an upper limit on the amount of time that could pass between vaccination and TM, making the representation that (to her knowledge) no Vaccine Program decision had ever held that there was a temporal cut-off when determining if a vaccine had caused injury. *Id.* at 102-03 ("I'm not positive that the vaccine court has to worry about all of this stuff, because there has never been an upper boundary for development of an autoimmune disease"), 149, 369.

Dr. Byers's testimony also touched upon the issue of the false lab result regarding Ms. Bender's IgM levels. She noted that the data from these results plainly revealed a discrepancy between the low IgM titers measured in Ms. Bender's cerebral spinal fluid ("CSF"), and the characterization of those results as high. Tr. at 46, 56-58. In order to double-check the result, Dr. Byers called the lab that had performed the CSF study, and obtained confirmation that the positive indicator was in error. *Id*. Dr. Byers described the significance of this finding, stating that had the IgM been positive, it would have indicated the existence of a prior recent infection that is known to be linked to TM. Tr. at 62. Thus, the absence of such evidence increased the likelihood that Ms. Bender's TM did not originate in that infection. *Id.* At the same time, Dr. Byers gave little weight to the implications of the positive IgG antibodies screen. She referenced several studies that showed that 70 percent of all young people were positive for IgG, which was usually linked back to a long-resolved infection, the evidence of which could stay in the body for years - thereby diminishing the possibility that some other prior infection had occurred close enough in time to have caused Ms. Bender's TM. *Id.* at 64, 70.

Significantly, Dr. Byers had difficulty identifying medical record support to corroborate Petitioner's assertions that the causation theory she outlined had actually occurred as theorized. She maintained throughout her testimony that the lack of an alternative explanation to her theory – such as in the form of evidence of a prior infection (like the debunked mycoplasma infection) – left only the conclusion that the vaccines were causative. Tr. at 46, 138, 373. But she admitted that Petitioner had been "completely asymptomatic" before her July 10, 2009 collapse incident, and that there was no record evidence that Petitioner had at this time or before any of the pro-inflammatory markers that would corroborate the "cytokine storm" concept. *Id.* at 139. Dr. Byers also agreed that none of Petitioner's treaters (including Dr. Kerr) ever identified a vaccine as causal of her TM, although she added that they may have been misled by their mistaken assumption that

the mycoplasma infection was causal. *Id.*at 139-40. And she allowed that TM could also be idiopathic in origin (meaning that no explanation for its genesis was possible). *Id.* at 138.

Dr. Byers acknowledged other limitations to the proof supporting her opinion. For example, she admitted that she could point to virtually no literature directly relevant to the Hep A or meningococcal vaccine, and that literature supporting an association between the Hep B vaccine and TM was not relevant to this case. Tr. at 156-57. She nevertheless maintained that this did not matter - since she based her opinion on the concept that *all* vaccines must "provoke protective immune reactions" if they are to have any effectiveness. Byers Rep. at 6; Tr. at 94-95. Accordingly, in her view the potency of vaccines generally is enough to cause a pathogenic autoimmune reaction in "an appropriately susceptible host." Byers Rep. at 6; *see also* Tr. at 88, 160 ("I am saying that any vaccine that is immunogenic enough to be approved by the FDA has the ability to cause an autoimmune disease"). In addition, Dr. Byers acknowledged that an item of literature Petitioner filed that generally discussed TM affirmatively stated that the "pathological hallmark" of TM is the presence of a "focal collection" of lymphocytes and monocytes – in other words, kinds of white blood cells - rather than cytokines. Tr. at 145; E. Frohman, et al., *Transverse Myelitis*, 363 N. Engl. J. Med. 564-72 (2010) ("Frohman"). However, she maintained that because Frohman also discussed that demyelination was a characteristic of TM, that article did not rebut her contentions of the role cytokines could play in the illness's pathogenesis. Tr. at 146.

2. Dr. Chone Ken Chen

Petitioner's second expert was a pediatric neurologist, Dr. Chen, who submitted two expert reports in this case and testified at hearing. *See* First Report, dated Aug. 28, 2014, filed as Ex. 25 ("Chen Rep."); Responsive Rep., dated June 5, 2015, filed on February 10, 2016 as Ex. 23 ("Chen Responsive Rep.")[26]; Tr. at 163-236.

Dr. Chen obtained his bachelor's and medical degrees from Boston University. Chen CV, filed as Ex. 24 (ECF No. 96); Tr. at 164-66. He completed a residency and internship in Pediatrics at Mount Sinai Medical Center in Manhattan and Queens, New York, followed by a residency and fellowship in neurology at New York University in Manhattan, New York. Chen CV at 2. Throughout his career, Dr. Chen has worked in various hospitals in the areas of adult and pediatric neurology, but is currently a pediatric neurologist with the Department of Pediatrics at New York University Downtown Hospital in Manhattan, New York. *Id*. at 1. In that role, Dr. Chen sees many patients, estimating that over his career he has treated hundreds of children and adults with neurological injuries. Chen Rep. at 1. Respondent pointed to an occasion when Dr. Chen's testimony was excluded, but it was not in the context of a vaccine case. Tr. at 200.

[26] Dr. Chen's responsive report was originally filed within a compilation of exhibits and documents submitted by compact disc on August 17, 2015, but subsequently refiled after current counsel's appearance in the case.

In his initial report, Dr. Chen reviewed Ms. Bender's medical records from the time of her initial presentation to KRMC, admitting that she was "asymptomatic of any respiratory or neurological disorders" for 40 days after vaccination. Chen Rep. at 2. He thereafter noted there was scientific support linking certain vaccines to autoimmune and/or demyelinating conditions, and that the manufacturer of the meningococcal vaccine Petitioner received had acknowledged in the relevant package inserts that it could be related to TM. *Id.* at 5, Ex. 25, Tab 22. He proposed that interaction of "multiple vaccine components" that Ms. Bender received in May 2009 was to blame for her TM. Chen Rep. at 6-8. He also suggested that in his reading of the medical records, because there was a "total lack of clinical change" in Petitioner's condition after her initial presentation, the autoimmune process that had resulted in her TM likely began "one to two weeks prior" to her collapse upon leaving the tour bus. *Id.* at 9.

Dr. Chen's 46-page supplemental report was designated as responsive to Respondent's initial expert report from Dr. Timothy Lotze (discussed below). In reacting to Dr. Lotze's interpretation of Ms. Bender's medical history, Dr. Chen stressed that the progressive evolution of lesions on Petitioner's spinal cord (as revealed in the MRIs performed in July 2009 and thereafter) suggested to him that the autoimmune processes that produced those lesions had to have begun before she first sought medical intervention on July 10th – and therefore her onset was likely closer in time to the administration of the vaccines in question. Chen Responsive Rep. at 4-6. He reached this conclusion despite the total lack of symptoms prior to the falling-down incident that impelled Petitioner to seek treatment. *Id.* at 9.[27] In his view, the initial lesions observed by MRI in July 2009 were "already quite advanced in development," meaning that the process resulting in her TM likely began far earlier. *Id.* at 11.

Beyond the above, Dr. Chen's second report simply expanded (at far greater length) on the same points made in his first – *i.e.,* that the package inserts and marketing materials associated with the meningococcal and Hep A vaccines all disclose TM as a reaction (Chen Responsive Rep. at 16-21), and that other vaccines have a similar capacity to cause the same injury (*Id.* at 23-36).[28]

[27] Dr. Chen's responsive report referenced the nonexistent "30-day (statutory) requirement for qualification of presumption of vaccine causation" discussed below. *See* Chen Responsive Rep. at 10.

[28] Dr. Chen also attempted to rebut Dr. Lotze's assertions that the Institute of Medicine ("IOM") had not found sufficient evidence with respect to the vaccines in question to deem them associated with TM, arguing that Dr. Lotze had misinterpreted the language used by the IOM. Chen Responsive Rep. at 12-13. I note that IOM evidence is often given credence in the Program. *Garner v. Sec'y of Health & Human Servs.,* No. 15-063, 2017 WL 1713184 (Fed. Cl. Spec. Mstr. Mar. 24, 2017). However, I do not find in this case that this particular kind of evidence is probative either way. I also note that *neither* Drs. Lotze nor Chen have immunological expertise – and because both parties have offered qualified immunologists, I have given testimony from non-immunologists on such matters significantly less weight.

At hearing, Dr. Chen performed a rambling narrative review of Ms. Bender's medical records, attempting to exclude a variety of other causes for her TM. Tr. at 186-88. He discussed in detail each of Ms. Bender's negative test results, opining (consistent with Dr. Byers) that because there were no signs of an ongoing infection between the date of her vaccination and onset, the vaccine could be assumed by process of elimination to have caused her TM. *Id.* at 185.

In addition, Dr. Chen reiterated his report's point that after her initial evaluation at KRMC, Ms. Bender's TM remained static in terms of severity and development. Tr. at 192. This lack of disease progression indicated to Dr. Chen that the autoimmune process affecting Ms. Bender had to have begun in the days *before* her admission to the hospital— thus, in his view, shrinking the timeframe between vaccination and onset. *Id.*; First Chen Rep. at 9. He deemed this as possibly meaning that Petitioner "met the 30-day requirement" for presumption under the Vaccine Act, although it is not clear to which portion of the Act he was intending to refer in so proposing. *Id.*[29]

Although Dr. Chen mostly attempted to provide an explanation of the course of Ms. Bender's TM, he also proposed an opinion regarding causation (a topic he was less qualified to opine upon than Dr. Byers). *See generally* Tr. at 200-25. In support, he referenced evidence from VAERS purportedly establishing that vaccines akin to what Petitioner had received could cause TM. Chen Rep. at 6; Tr. at 217-18. He also pointed out (consistent with Dr. Byers's arguments) that the package inserts included with the relevant vaccines by their manufacturers acknowledge the possibility of TM as a side effect. *See generally,* Chen Rep. at 8; Chen Responsive Rep. at 23-36; Tr. at 205-06.

C. *Respondent's Experts*

1. Dr. Timothy Lotze

The first of Respondent's experts to testify was Dr. Lotze, a pediatric neurologist, who submitted a single written report. Report, dated Feb. 12, 2015, filed as Ex. A (ECF No. 67) ("Lotze Rep."); Tr. 238-76.

Dr. Lotze obtained his bachelor's degree from Texas A&M University in College Station, Texas, followed by his medical degree at the University of Texas, San Antonio. Lotze CV, filed as Ex. B (ECF No. 67). Thereafter, he completed two residencies and an internship at The Ohio

[29] It may be that Dr. Chen was advancing the argument that the claim herein is akin to a Table Claim, for which causation is presumed when sufficient evidence is adduced to meet the requirements of particular claims. But TM is *not* included in the injuries specified for either of the vaccines in question – or *any* other vaccine for that matter. In addition (and ignoring for the moment Dr. Byers's incorrect statements that there is effectively no temporal limit for a Program claim to the timeframe between onset and vaccination), there is no requirement - whether set forth in the Act or the decisions of any special master or controlling federal court ruling reviewing such decisions – that a vaccine injury claim establish onset within 30 days of receipt of the vaccine at issue.

State University, in Columbus, Ohio, finishing his education with a residency in Child Neurology at Baylor College of Medicine in Waco, Texas. *Id*. at 1. He was then hired as a faculty member at the Baylor College of Medicine, where he is currently employed. *Id*. In his present capacity he treats children, with a special focus on multiple sclerosis and muscular dystrophy. Tr. at 239. Dr. Lotze estimated that he has seen around 150 children with TM. *Id*.

Although Dr. Lotze acknowledged that he lacked specific training or expertise in immunologic matters, he opined that Ms. Bender's TM was not related to either of the vaccinations she received. Tr. at 242. After reviewing all of Ms. Bender's medical records, Dr. Lotze concluded that her TM was instead more likely than not idiopathic. *Id*. He admitted that the IgM reading relied upon initially by treaters was incorrect, but stated that it still could not be determined whether or not Ms. Bender's TM was connected with a prior mycoplasma infection, as the testing for the titers was never performed again in her treatment. Lotze Rep. at 4. Otherwise, Dr. Lotze could not identify a cause of Ms. Bender's TM, nor was he aware of any association between TM and vaccination set forth in any medical or scientific literature. *Id*.

Dr. Lotze testified about the timing of Petitioner's TM onset. In his understanding, because TM is considered to be an autoimmune process, it needs an environmental trigger to cause the inflammation leading to the condition. Tr. at 246. He stated that he would expect a reaction to such a trigger to occur within three weeks – sooner than what Ms. Bender experienced. *Id*. at 251. Onset of TM would not likely occur longer than three to four weeks after an infectious exposure, making a 42-day time interval too long to implicate the vaccines Ms. Bender had received in causing her TM. *Id.* at 250-51.

In so arguing, Dr. Lotze took specific issue with Dr. Chen's proposal that the progression of lesions observed from the two sets of MRIs performed between July 10 and 14, 2009, suggested some kind of subclinical process was under way before July 10th. On the contrary - Dr. Lotze maintained that the rather significant progression from the time of the first to the second MRI was actually strong evidence of how acute and recent Ms. Bender's TM onset was – not that it had to have been ongoing for some time, especially with the absence of other neurologic symptoms pre-dating her acute loss of below-waist sensation on July 10, 2009. Lotze Rep. at 3. As he specifically stated in his report,

> comparing the MRI spine imaging between the initial study performed on July 9 [sic][30] and the second study on July 14, it was demonstrated that there was an extension of the lesion from a single vertebral segment at T11-12 on the first study to a long cord lesion beginning at T8 and extending through the remainder of the

[30] The medical record clearly establishes that the first MRIs were performed on July 10 – although this error in Dr. Lotze's report does not detract from his point about the nature of the progression of Petitioner's TM.

> spinal cord on the second study. *This suggests that her autoimmune myelitis was more recent in its onset.*

Id. at 3 (emphasis added).

Dr. Lotze also rejected Petitioner's contention that the Agmon-Levin article was persuasive evidence of an association between a variety of vaccines and TM. Tr. at 253. That article, he testified, listed case reports of incidences of TM after vaccination, but he opined that there were other, more likely, explanations for the associations found in the article. *Id*. at 254. For example, one of the case reports Agmon-Levin considered was from a child with an ongoing autoimmune condition *known* to produce TM. *Id*. Another report was from a patient who had received the oral polio vaccine - a live vaccine known to have the potential to cause poliomyelitis, the kind of direct infection that could in turn cause TM. *Id*. at 254-55. These case studies therefore were distinguishable, and did not provide reliable baselines for determining the timeframe for post-vaccination TM.

2. Dr. Thomas Forsthuber

Respondent's second expert was Dr. Thomas Forsthuber, an immunologist. Dr. Forsthuber provided testimony at hearing and produced one expert report in the case, to which was appended several items of medical or scientific literature.[31] *See* Report, dated Jan. 19, 2017, filed as Ex. C ("Forsthuber Rep."); Tr. at 277-361.

Dr. Forsthuber received his medical degree from the University of Tübingen in Germany and then completed a post-doctoral fellowship in immunology at the University of California, Los Angeles. Tr. at 277; Forsthuber CV, filed as Exhibit D (ECF No. 115). He completed an additional post-doctoral fellowship at Case Western University in Cleveland, Ohio. Forsthuber CV at 2; Tr.

[31] At hearing, Dr. Byers (called by Petitioner for her rebuttal case) objected that she had not had the chance to "see" certain articles involving animal studies that Dr. Forsthuber referenced in his testimony. Tr. at 386. She later clarified that she had only reviewed those items filed in connection with his report involving human studies, because they were directly "cited" in his expert report. *Id.* at 387.Then, upon further questioning by Petitioner's counsel, Dr. Byers suggested in fact that she had seen (or had the opportunity to review) *all* items filed in connection with Dr. Forsthuber's report, but continued to maintain that Dr. Forsthuber referenced studies in his testimony not filed with his report. *Id.* at 389. Respondent for his part denied that Dr. Forsthuber made any argument as to items not filed (*Id.* at 386), and in her post-trial brief Petitioner pointed to only one article that she alleges was referenced but never filed. *See* Petitioner's Post-Hearing Brief, dated April 28, 2017 (ECF No. 121), at 10 n.12 (referencing the "Miller" article without citation).

Having reviewed the transcript, I do not find that Dr. Forsthuber made any argument regarding a particular item of literature that was never filed. At best (and like Dr. Byers), he made some assertions that were reliant on his immunologic expertise. Moreover, the "Miller" article referenced by Petitioner was only referred to in passing as "one of two articles" published at the time of Lehmann – and Dr. Forsthuber, who co-authored Lehmann, limited his testimony to Lehmann. Tr. at 300-01. I also reject Dr. Byers's contention that anything was sprung upon her at trial. Dr. Forsthuber's report was filed nearly three weeks before trial – and after Petitioner filed an expert report from Dr. Byers without first seeking my approval, in a case that was over five years old at the time.

at 278. He became a member of the faculty at the University of Texas, San Antonio, and began performing research in immunology and now runs a research lab that does T cell biology work and B cell immunology. *Id*. In addition, Dr. Forsthuber has over 75 publications (reviews and book chapters) in the areas of T cell immunology and autoimmune diseases. Forsthuber Rep. at 1. Dr. Forsthuber is board certified in anatomical and clinical pathology. Forsthuber CV at 2.

Dr. Forsthuber opined that the vaccines Ms. Bender received played no causal role in the development of her TM. Tr. at 280. He noted (as had Dr. Lotze) that he could identify no literature he deemed reliable associating either the meningococcal or Hep A vaccines with TM. Forsthuber Rep. at 5. Dr. Forsthuber was aware of a limited number of case studies linking TM to the wild meningococcal bacterial infection, but in his view the rarity of such cases suggested that a meningococcal vaccine (which because of its weakness must be conjugated with diphtheria toxoid to raise its immunogenicity) was even less likely to have any association. Tr. at 324-25. He also rejected Petitioner's arguments that associations demonstrated between vaccines and *other* autoimmune diseases, like Guillain-Barré syndrome ("GBS"), should be given evidentiary weight, noting that in the case of GBS the disease was mediated by B cell production of autoantibodies rather than by T cells, as in the case of TM. *Id.* at 326, 345.

Dr. Forsthuber next challenged Petitioner's overarching theory that cytokines like IL-6 inherently induced by vaccination were central to the pathogenesis of her TM. While he admitted that such cytokines likely do play a role in TM's exacerbation, he disagreed that they alone were *sufficient* to initiate a process resulting in TM. Tr. at 307, 309. He claimed he was unaware of any valid scientific or medical studies demonstrating that the introduction of large amounts of proinflammatory cytokines was enough to cause CNS autoimmune diseases. *Id.* at 310. Dr. Forsthuber also rejected Dr. Byers's reliance on Kaplin for such points. Forsthuber Rep. at 17. In his view, Kaplin showed that the cytokine IL-6 was *not* able by itself to instigate a pathologic process leading to TM, and therefore could not be identified as a mechanism of bystander activation, even if vaccination could cause upregulation of such cytokines. *Id.*; Tr. at 308 (IL-6 at best a component in the process leading to TM, but cannot alone replicate an inflammatory process). In addition, the authors of Kaplin had injected IL-6 directly into the spinal cord, not in the periphery (where it would most likely develop in response to a vaccination administered in one's arm), confirming only the "regional" importance of such cytokines. Tr. at 308.

At bottom, Dr. Forsthuber maintained, the question was whether IL-6 (or any cytokines for that matter) could be considered the direct cause of an autoimmune pathologic process, or merely an "effector mechanism" *responsive* to prior T cell action, with Dr. Forsthuber favoring the latter explanation. He maintained that reliable scientific literature more credibly suggested that autoimmune processes were usually "antigen-specific," and that any cytokine release subsequently associated with inflammation would be "transient, of low titer, and [would] rarely progress to autoimmune diseases" not already instigated by a direct viral attack. Forsthuber Rep. at 16.

Dr. Forsthuber contested the proposed immunological mechanisms suggested by Dr. Byers—bystander activation and epitope spreading – arguing that neither was supported by sufficient medical or scientific evidence to constitute reliable explanations for how TM could occur in connection with the relevant vaccinations.[32] He began by agreeing with Dr. Byers that molecular mimicry could not explain the mechanism for the autoimmune process resulting in Petitioner's TM, leaving only the two other proposed mechanisms. Tr. at 280-81. In discussing them, Dr. Forsthuber relied on his direct research experience regarding T cells, especially in light of technological advances permitting better understanding of the function of T cells in the immunologic process. Tr. at 286.

Dr. Forsthuber defined bystander activation as "activation of T lymphocytes in the absence of their specific signals" from a presenting foreign antigen, resulting in a "nonspecific" activation of those immune system cells in a disease process. Tr. at 282. Bystander activation was discovered when tissue being attacked by a disease process was found to contain T cells not specific to the attacking infectious agent. *Id.* at 284, 293. The researchers first responsible for the theory of bystander activation had been forced to rely on imprecise detection methods, thereby misleading them into believing that the majority of T cells contributing to an ongoing inflammatory process were likely nonspecific. *Id*. at 284. More recent innovations in technological detection methodologies (in particular, "tetramer staining"[33]), however, had convinced researchers that "the majority of T cells in an infection are specific for the antigen," meaning that "bystander activation is occurring to a degree, but to a lesser degree" than previously believed. Tr. at 287; 284-86.

As a result, Dr. Forsthuber proposed that the entire concept of bystander activation as possibly explaining the pathogenesis of TM was lacking a key component. Tr. at 286 ("all this fuss about bystander activation turned out to be a lot of hot air"). T cell activation *specific* to a presenting foreign antigen at the outset of an alleged autoimmune process was required for bystander activation to even occur. *Id*. at 355.[34] Those nonspecific T cells found at the situs of a disease process, moreover, were either transiently there ((Tr. at 292) "[U]sually, if they don't see

[32] Besides addressing Dr. Byers's contentions, part of Dr. Forsthuber's report was devoted to rebutting several of Dr. Chen's points about causation. *See, e.g.*, Forsthuber Rep. at 6 (attacking Dr. Chen's contention that receipt of multiple vaccines at once could enhance their pathogenic impact). I do not address these aspects of Dr. Forsthuber's opinion at length, however. Not only were they largely not raised at hearing, but also it is the contentions of Petitioner's immunologist expert, Dr. Byers, that form the core of Petitioner's causation theory (and therefore warrant more serious consideration than Dr. Chen's unsupported speculation regarding causality).

[33] Tetramer staining involves "a reagent that highly specifically recognized a T cell that is specific for a particular virus . . . . [i]t is really a peptide that these T cells would recognize, and then they have a soluble image C molecule that this peptide is clued into, and then they attach a color to this and now you have a molecule that's very sensitive and recognized not all the T cells, but specifically T cells, for example, that would recognize influenza." Tr. at 285.

[34] In addition, Dr. Forsthuber noted that, as the literature establishes, bystander activation is known to occur most efficiently with CD8 positive T cells - but autoimmune conditions such as TM are posited to be caused by CD4 positive T cells, thus further reducing the likelihood that bystander activation was applicable to this case. Tr. at 287-88.

their specific antigen, all they do is say hi, and thank you, and they leave the tissue again"), or had nothing to do with encouraging the overall inflammatory disease process. *Id.* at 294.

In discussing bystander activation, Dr. Forsthuber was critical of the scientific support offered by Petitioner and her experts in support of the mechanism. Murali-Krishna, in Dr. Forsthuber's reading, actually *confirmed* that the primary antigens responsible for inducing autoimmune responses were highly specific in their targets, impacting the number of specific T cells rather than bystanders, and thereby undermining the notion that nonspecific immune cells played a large role in furthering an autoimmune response. Forsthuber Rep. at 16-17; Tr. at 287, 289, 292; Murali-Krishna at 185 ("this study provides definitive evidence that the majority of CD8 T cells responding to a viral infection are antigen-specific"). Thus, although Murali-Krishna observed that nonspecific T cells contribute in part to the destruction of self tissues in an autoimmune process, they did so only *after* being activated by an initial infectious process – underscoring the need for a cross-reactive process to have already begun (whether via molecular mimicry or direct infection) before bystander activation would begin. Tr. at 293.

Dr. Forsthuber also noted that other items of literature further demonstrated the extent to which the bystander activation theory had been called into question. For example, he discussed a study seeking to determine whether recipients of the flu vaccine experienced an increase in antibodies not specific to the flu virus – whether it "would boost a pre-existing immune response against another antigen" (Tr. at 295) – but which found that this did not occur. M. Delaney, et al., *Humoral Immunomodulatory Effect of Influenza Vaccine in Potential Blood Donors: Implications for Transfusion Safety*, 21 Transfus. Med. 6, 378-84 (2011), filed as Ex. C, Tab 7 (ECF No. 114-8). Another test involving an animal model sought to determine "whether vaccination with different antigens would boost immune responses to unrelated antigens." Tr. at 295; F.E. Lee, et al., *Circulating Human Antibody-Secreting Cells During Vaccinations and Respiratory Viral Infections Are Characterized by High Specificity and Lack of Bystander Effect,* 186 J. Immunol. 9, 5514-21 (2011), filed as Ex. C, Tab 13 (ECF No. 115-3) ("Lee"). Lee too found no such boost to nonspecific immune response, and Dr. Forsthuber argued that the article "strongly suggests that if you have an infection with – or vaccination with one agent, it has a very limited capacity of inducing immune responses to unrelated antigens." Tr. at 297; Lee at 5517.

For such reasons, Dr. Forsthuber rejected Petitioner's contention that bystander activation could provide a reliable mechanism by which vaccination could result in TM. As a result, Dr. Byers's acknowledgment that molecular mimicry as a general mechanism could not be applied to the circumstances of this case was harmful to her embrace of bystander activation as an alternative mechanism. Some "initial pathogenic T cell response in the CNS" would be required to begin the process of activating the nonspecific autoreactive T cells, but "what activates pathogenic T cells to begin with?" Tr. at 354-55. In Dr. Forshuber's view, Dr. Byers had not adequately answered that question. Dr. Forsthuber made another broad point regarding the applicability of bystander

activation to an autoimmune disease like TM in light of Petitioner's theory about the cytokine-driven nature of Petitioner's disease. He maintained that bystander activation was not meaningful in such a context, because "a T cell that causes autoimmune pathology . . . doesn't just start to produce pathogenic cytokines on its own," but instead needs to "see," or cross-react with, the self antigen before cytokines are part of the process (and thus again, there must be some T cell specificity for autoimmunity to occur in Dr. Forsthuber's view). *Id.* at 289.

In response to Dr. Byers's second proposed causal mechanism, epitope spreading, Dr. Forsthuber pointed out he was well qualified to opine on the topic, as he was one of the researchers responsible for initial evaluation of the concept -- and a co-author of the Lehmann article cited favorably by Dr. Byers. Tr. at 300, *citing* Lehmann (Dr. Forsthuber identified as one of three authors). As he described it, epitope spreading occurs when autoimmunity is initiated by a specific set of T cells, those cells precipitate inflammation in a tissue, and the inflammatory process in turn causes the release of additional antigens in that location, ultimately causing a new set of autoimmune T cells to activate, go to the tissue/site of ongoing inflammation, and cause further damage. *Id*. at 302; Forsthuber Rep. at 20. Epitope spreading is thus understood to be "important in sustaining this autoimmune response or triggering relapses of this autoimmune response." Tr. at 303. But it is properly viewed as a "continuation" of an already-underway autoimmune process – not its initiation. *Id.* at 303, 344.

Based upon the above, Dr. Forsthuber questioned the applicability of epitope spreading as a potential mechanistic explanation relevant to this case. Tr. at 355. If epitope spreading could explain the process by which Petitioner's vaccines injured her, he maintained, there would need to be some kind of "major" initial clinical manifestation – for example, "enough tissue damage in the CNS for the antigen to leak out, and/or trigger epitope spreading." *Id.* at 356. But here there was only evidence of acute onset of TM. Dr. Byers's characterization of the concept of epitope spreading, moreover, was in Dr. Forsthuber's view nothing more than a description of molecular mimicry, since her conceptualization of the mechanism involved a presenting antigen *followed* by activation of nonspecific T cells. *Id.* at 303. But because Dr. Byers had already conceded that she could not provide an antigen-specific mechanism to explain TM's alleged vaccine-induced pathogenesis herein, epitope spreading failed as an alternative explanatory mechanism for Ms. Bender's TM because it inherently relied on a molecular mimicry process occurring *first,* to initiate the autoimmune process. *Id.* at 357.

Dr. Forsthuber also referenced[35] in his testimony a recent epidemiologic study involving the propensity of a number of vaccines to cause TM. *See* R. Baxter, et al., *Acute Demyelinating*

[35] I take note of the fact that Dr. Forsthuber is not a statistician or epidemiologist, and therefore his testimony about the reliability of Baxter must be weighed against his lack of specific expertise on such topics. At the same time, however, I note that *no* experts who testified in this matter possessed that kind of specialized knowledge – putting all of them on a level playing field, so to speak, when it came to opining as to the reliability of epidemiologic evidence.

Events Following Vaccines: A Case-Centered Analysis, 63 Clinical Infectious Diseases 1456-61 (2016), filed as Ex. C, Tab 4 (ECF No. 114-5)("Baxter"), Tr. at 321-22.[36] In Baxter, researchers considered all cases of TM (as well as acute disseminated encephalomyelitis ("ADEM")) in the United States that were recorded to have occurred in a population of nearly 64 million vaccine dose recipients, including over 3.4 million Hep A doses, and 1.5 million meningococcal vaccine doses comparable or identical to Menactra. Baxter at 1457. The study was case-centered, meaning it compared vaccination of each studied case to vaccination of all matched persons in the study population, looking at two specific exposure intervals of 28 and 42 days after vaccination. *Id*. at 1456. No statistically significant heightened risk of TM could be seen in either 5-28 days following vaccination (as compared to the nine months after), or the longer 2-42 day time period. Dr. Forsthuber admitted that Baxter was not a "randomized study," and therefore could not be cited as definite proof that the vaccines relevant herein could never be associated with TM in the studied time periods, but he otherwise expressed the view that it was reliable and relevant evidence. Tr. at 350-52.[37]

With respect to alternative causes, Dr. Forsthuber emphasized Ms. Bender's initial CBC results, which (given the elevated white blood cell counts and decreased lymphocytes) suggested to him some concurrent infectious process was most likely to blame for her TM, despite the fact that no other evidence of infectious disease was found. Forsthuber Rep. at 2; Tr. at 329.[38] In so arguing, Dr. Forsthuber maintained that (contrary to Dr. Chen's argument that Ms. Bender's demyelination process had to have been under way for some time prior to her first clinical manifestation of a neurologic symptom) such test results underscored the extent to which the unknown cause of Petitioner's TM likely occurred close in time to her presentation – not six weeks prior. Forsthuber Rep. at 9.

[36] Baxter was similarly, if briefly, mentioned by Dr. Lotze. *See, e.g.,* Tr. at 248-49.

[37] Dr. Byers attempted to address Baxter in her opinion. She maintained that, given TM's rarity, *no* epidemiologic study could be powered enough (i.e. have enough subjects) to measure its post-vaccination incidence accurately. Tr. at 72. She also contended that studies like Baxter were likely just a collection of "case reports" rather than a controlled randomized study – although this is a mischaracterization of Baxter's actual methodology and structure. *Id.* at 125; Baxter at 1458 (explaining that "[w]e identified all cases in the vaccinated study population. We compared each case to all similar (by age, sex, and VSD site) vaccines who were in the study population on the diagnosis date of the case. We compared the cases to the general population, with respect to whether or not their vaccination occurred during the exposure interval. Thus, the method is equivalent to a matched case-control study, except that it utilizes all available matched controls who received the same vaccine type, rather than just a sample of them.").

[38] Dr. Forsthuber also accepted the fact that the reported high IgM titer reading was incorrect, but proposed that the positive IgG reading still allowed for the conclusion that Ms. Bender had experienced a mycoplasma infection closer in time to her initial onset than vaccination (since the short half-life of IgM did not preclude a mycoplasma infection in the two weeks after vaccination). Forsthuber Rep. at 12. This argument is intriguing, but ultimately speculative, absent other corroborative evidence of a prior infection close enough in time to Ms. Bender's initial symptoms to be associated.

Finally, Dr. Forsthuber discussed what he deemed to be reasonable timeframes for onset of a vaccine-induced TM. Based on science he deemed reliable (epidemiologic studies considering known viral causes of TM), plus his own experience, he proposed up to three to four weeks to be a reasonable timeframe for onset. Forsthuber Rep. at 8; Tr. at 313. Once T cell activation necessary for an autoimmune process had begun, Dr. Forsthuber would expect the immune response to mount rapidly, likely peaking two weeks from the inciting event. *Id.* at 318, 347-49. After the 30th day, however, he would expect the immune response to be dwindling greatly (and thus no longer possessing the same pathogenic capacity). *Id.* at 349 ("an activated T cell does not live forever"). The production of cytokines post-vaccination would be especially rapid, occurring within days. *Id.* at 319.

As a result, Dr. Forsthuber rejected the proposition that 42 days was a reasonable onset timeframe. Tr. at 341 ("the immune response would not keep expanding at that point"). In response to the Agmon-Levin article, which proposed a potentially longer timeframe for TM's development after several different vaccinations, Dr. Forsthuber (like Dr. Lotze) looked at the individual case examples that were relied upon to create the chart, but found reason in each case to question their scientific reliability (for example, because the subject of a case study had some identified cofactor that might have caused the TM, or because of misdiagnosis). *Id.* at 315-17. He also noted that Agmon-Levin did not involve the relevant vaccines herein. *Id.* at 317.[39]

III. Procedural Background

After initiating this action (originally assigned to former Special Master Hastings) in October 2011, Petitioner began filing medical records and securing an expert witness, a process that became slow, delaying the progression of the case. Nonetheless, Respondent filed his Rule 4(c) Report on July 25, 2012. For a year thereafter Petitioner looked for an expert but was ultimately unsuccessful. Eventually, Petitioner's attorney chose to withdraw from the case on February 2, 2014.[40] Thereafter, the case was reassigned to me and Petitioner became *pro se*.

After holding a status conference with Petitioner on June 30, 2014, I issued an order directing her to file an expert report in six months. *See* Scheduling Order dated July 1, 2014. Petitioner was able to file her expert report from Dr. Chen early, on September 2, 2014. Over the next year, Respondent filed his expert report from Dr. Lotze, Petitioner sought to retain an expert to provide a supplemental expert opinion, and the parties began informal settlement negotiations.

[39] Dr. Forsthuber admitted as well that Baxter did consider the incidence of certain demyelinating conditions in a timeframe up to 42 days, but pointed out that it found no risk in that longer period. Tr. at 322.

[40] Former counsel expressed the desire to withdraw a year earlier, on February 3, 2013, but Petitioner's inability to obtain new counsel, a dispute in the request for interim attorney's fees and costs, and a stay in the case due to the 2013 government shutdown further delayed the case's progress.

On December 22, 2015, Petitioner's current attorney entered an appearance in the case. Shortly thereafter, on January 13, 2016, the parties indicated in a joint status report that settlement was not likely to occur, and I scheduled a two-day entitlement hearing for February 9-10, 2017. *See* Joint Status Report, dated Jan. 13, 2016 (ECF No. 81); Prehearing Order, dated Mar. 22, 2016 (ECF No. 86). After the filing of additional expert reports referenced above and medical literature from both parties, the hearing was held as scheduled. Post-hearing briefs were filed between the second half of April and end of June.

IV. Original Entitlement Decision and Disposition of Motion for Review

I issued a decision denying compensation on October 6, 2017. My adjudication of the claim arose from the conclusion that Petitioner had failed to carry her burden of proof by a preponderance of the evidence – that there was simply insufficient reliable evidence to support Petitioner's conclusion that the two vaccines she received were *themselves* reasonable explanations for her TM. *Bender v. Sec'y of Health & Human Servs.*, No. 11-693V, 2017 WL 5381628, at *19 (Fed. Cl. Spec. Mstr. Oct. 6, 2017).

Most relevant to the matter now, my Decision noted that Dr. Byers had made a "significant concession" relevant to her theory when she "unequivocally agreed that molecular mimicry was *not* a plausible biologic mechanism at work herein." *Id.* at *5. Without molecular mimicry as a viable mechanism for the instant case, the plausibility of Petitioner's other proposed mechanisms, bystander activation and epitope spreading, was significantly diminished, because while those mechanisms may play a contributory role in the pathogenesis of an autoimmune condition like TM, a preceding condition for these mechanisms was an autoimmune response to a specific antigen presented by a vaccine component that tricks the immune system into that response. *Id.* Because I had ruled out molecular mimicry and because there was no evidence suggesting any other direct infectious process occurred, I found that Petitioner's theories of causation relied too heavily on more general points between the relationship between vaccines and autoimmune illness to be deemed reliable.

On November 3, 2017, Petitioner filed her motion for review of my Decision. ECF No. 129 ("MFR"). Petitioner noted two specific objections to my Decision – first, she contended that "[i]t was arbitrary and capricious for the Special master to based [sic] his *Althen* prong analysis on the significant misconstruction and mischaracterization of Petitioner's expert immunologist, Dr. Vera Byers', testimony"; and second that "[i]t was arbitrary and capricious for the Special master to impermissibly raise Petitioner's burden of proof by improperly requiring specific medical literature." MFR at 7.

Regarding the first point, Petitioner pointed out specific testimony in which Dr. Byers stated that she believed epitope spreading to be "molecular mimicry on a very individual basis." *Id.* at 9. Petitioner buttressed her argument by citing to testimony from Dr. Forsthuber in which he mentioned that he believed Dr. Byers was positing a theory of molecular mimicry only when discussing epitope spreading. *Id.* Thus, Petitioner contended that I misconstrued Dr. Byers' testimony.

The Court of Federal Claims agreed with Petitioner's argument. In remanding the matter back to me, the Court noted that "[g]iven Dr. Byers' distinction between two types of molecular mimicry - - generalized 'widespread molecular mimicry' and individualized molecular mimicry, this Court finds that Dr. Byers did not make the broad concession about the inapplicability of molecular mimicry that the Special Master attributed to her." Remand Order at *9. The Court further noted that in light of the need to reevaluate Dr. Byers' testimony, I was to reassess the relevant medical literature and the absence of test results, as well as my conclusion that Petitioner had failed to make the requisite temporal connection under *Althen* prong three. *Id.*

V. Applicable Law

A. *Petitioner's Overall Burden in Vaccine Program Cases*

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury" – *i.e.*, an injury falling within the Vaccine Injury Table – corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).[41] In this case, Petitioner does not assert a Table claim.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d

[41] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd* 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a Non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen*: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1278.

Each of the *Althen* prongs requires a different showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015).

In discussing the evidentiary standard applicable to the first *Althen* prong, many decisions of the Court of Federal Claims and Federal Circuit have emphasized that petitioners need only establish a causation theory's biologic plausibility (and thus need not do so with preponderant proof). *Tarsell v. United States*, 133 Fed. Cl. 782, 792-93 (2017) (special master committed legal error by requiring petitioner to establish first Althen prong by preponderance; that standard applied only to second prong and petitioner's overall burden); *Contreras*, 121 Fed. Cl. at 245 ("[p]lausibility . . . in many cases *may* be enough to satisfy *Althen* prong one" (emphasis in

original)), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017); *see also Andreu*, 569 F.3d at 1375. At the same time, there is contrary authority from the Federal Circuit suggesting that the same preponderance standard used overall in evaluating a claimant's success in a Vaccine Act claim is also applied specifically to the first *Althen* prong. *See*, e.g., *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1350 (Fed. Cir. 2010) (affirming special master's determination that expert "had not provided a "reliable medical or scientific explanation" *sufficient to prove by a preponderance of the evidence a medical theory* linking the [relevant vaccine to relevant injury]") (emphasis added). Regardless, one thing remains: petitioners always have the ultimate burden of establishing their Vaccine Act claim *overall* with preponderant evidence. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted); *Tarsell*, 133 Fed. Cl. at 793 (noting that *Moberly* "addresses the petitioner's overall burden of proving causation-in-fact under the Vaccine Act" by a preponderance).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs*., 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct – that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record – including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Dept. of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot.*

for review den'd, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. *Law Governing Analysis of Fact Evidence*

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Human Servs*., 3 F.3d 415, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records that are created contemporaneously with the events they describe are presumed to be accurate and "complete" (i.e., presenting all relevant information on a patient's health problems). *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"), *aff'd*, *Rickett v. Sec'y of Health & Human Servs*., 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked propositions that (i) sick people visit medical professionals; (ii) sick people

honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Human Servs.*, No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Human Servs.*, 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d at 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms").

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Human Servs.*, No. 03-1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony – especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; *see also Murphy v. Sec'y of Health & Human Servs*., 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Human Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Human Servs*., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Human Servs*., No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *La Londe v.*

Sec'y of Health & Human Servs., 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. *Analysis of Expert Testimony*

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs*., 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993). *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial for a (such as the district courts). *Daubert* factors are usually employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable and/or could confuse a jury. In Vaccine Program cases, by contrast, these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs*., 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness and reliability of expert testimony has routinely been upheld. *See, e.g.*, *Snyder*, 88 Fed. Cl. at 742-45. In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743

(quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 91997)); *see also Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 Fed. App'x 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

D. *Consideration of Medical Literature*

Both parties filed medical and scientific literature in this case, but not every filed item factors into the outcome of this decision. While I have reviewed all of the medical literature submitted in this case, I discuss only those articles that are most relevant to my determination and/or are central to Petitioner's case – just as I have not exhaustively discussed every individual medical record filed. *Moriarty v. Sec'y of Health & Human Servs.*, No. 2015-5072, 2016 WL 1358616, at *5 (Fed. Cir. Apr. 6, 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted); *see also Paterek v. Sec'y of Health & Human Servs.,* 527 F. App'x 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to – and likely undermines – the conclusion that it was not considered").

ANALYSIS

I. Overview of TM and Case Law Relevant to Vaccines at Issue

TM is an autoimmune inflammatory condition causing damage to the spinal cord, which can produce neurological deficits with sensory loss in the extremities. Tr. at 241. It is understood to be mediated by pathogens that cause demyelination. *See* V. Wolf, et al., *Pediatric Acute Transverse Myelitis Overview and Differential Diagnosis*, 27 J. of Child Neurology 11:1426-36 (2012), filed as Ex. A, Tab 1 (ECF No. 67) ("Wolf"); Frohman at 564.

TM most often occurs after direct infection (and in some cases, vaccination), or as the secondary result of an acquired or underlying autoimmune disease, although up to a third of cases are deemed idiopathic in origin. Frohman at 564. Acute TM is so characterized because of its abrupt onset of motor and autonomic dysfunction. Wolf at 1426. Diagnosis of the condition typically comes after inflammation is revealed on a spinal MRI, as well as evidence of

inflammation derived from CSF analysis. Tr. at 242. Both sides' experts agreed that TM is likely mediated by T cells (something that is not true of all autoimmune diseases). Significantly for present purposes, and as noted in Frohman, "[t]he observation that systemic infection or immunization precedes many cases of [TM] suggests that mechanisms *such as molecular mimicry* and the development of autoantibodies may play roles in the pathogenesis of the syndrome." Frohman at 564-65 (emphasis added).

Petitioner filed an article written by one of Ms. Bender's treaters, Dr. Kerr, discussing some of the understood immune system-derived sources of TM. D. Kerr, et al., *Immunopathogenesis of Acute Transverse Myelitis*, 15 Curr. Opin. Neurol. 339-47 (2002), filed as Ex. 30, Tab 13 (ECF No. 104-1) ("Kerr"). Kerr notes that it has been "widely reported" that TM can be a post-vaccination event. Kerr at 340. However, Kerr goes on to cite only two case reports for this proposition – neither of which involve the vaccines in question, and in which each onset occurred no later than two to ten days post-vaccination. *Id.* at 340-41. As a result, Kerr cautions that "it is entirely possible that [the] two events occurred in close proximity by chance alone." *Id.* at 341. In addition, although Kerr discusses the mechanisms of bystander activation and epitope spreading, it suggests that either would occur only *after* molecular mimicry or some other instigating insult (i.e., a direct infection) had first initiated an autoimmune cross-reaction. *Id.* at 343.

Vaccine Program petitioners have successfully established that a number of different vaccines (*not* including the Hep A or meningococcal vaccines) were causally connected to their subsequent development of TM. *Schmidt v. Sec'y of Health & Human Servs.,* No. 07-20V, 2009 WL 5196169 (Fed. Cl. Spec. Mstr. Dec. 17, 2009) (influenza vaccine and TM); *Hargrove v. Sec'y of Health & Human Servs.*, No. 05-0694, 2009 WL 1220986 (Fed. Cl. Spec. Mstr. Apr. 14, 2009) (Diphtheria-tetanus-acellular pertussis vaccine and TM); *Raymo v. Sec'y of Health & Human Servs.*, No. 11-0654V, 2014 WL 1092274 (Fed. Cl. Spec. Mstr. Feb. 24, 2014) (tetanus diphtheria-acellular-pertussis vaccine and TM). Significantly, these cases often involve a petitioner claiming a mechanism *not* at issue in this case – molecular mimicry between components of the vaccine and protein sequences in the myelin basic protein ("MBP") that is a primary component of nerves. *See, e.g., Raymo*, 2014 WL 1092274, at *19 ("[b]ecause many cases of [TM] are considered to be immune-mediated, molecular mimicry is often considered to be the likely mechanism of injury"). However, other mechanisms parallel with what Petitioner argues herein, like bystander activation, have also been deemed scientifically reliable in explaining the biologic mechanism behind TM. *Id.* at *20 (discussing bystander activation).

I have identified no published reasoned decisions (meaning cases in which a special master wrote an opinion, as opposed to cases the parties settled) that directly involve the two vaccines at issue herein and TM. Indeed, there are only a handful of published decisions involving the Hepatitis A or meningococcal vaccines *at all* relevant to this claim, and they provided limited guidance. *See generally Giannetta v. Sec'y of Health & Human Servs.,* No. 13-215V, 2017 WL

4249946 (Fed. Cl. Spec. Mstr. Sept. 1, 2017) (meningococcal vaccine found to be causal of petitioner's multiple sclerosis); *Kennedy v. Sec'y of Health & Human Servs.,* No. 09-474V, 2012 WL 1929801 (Fed. Cl. Spec. Mstr. May 8, 2012) (petitioner succeeded in demonstrating that Tdap and meningococcal vaccines caused his ADEM); *Ramsey v. Sec'y of Health & Human Servs.,* No. 07-786V, 2011 WL 2463532 (Fed. Cl. Spec. Mstr. May 27, 2011) (Hep A vaccine not shown to cause ADEM or limbic encephalitis); *Veryzer v. Sec'y of Health & Human Servs.,* No. 06-522V, 2011 WL 1935813 (Fed. Cl. Spec. Mstr. Apr. 29, 2011) (Hep A vaccine not successfully established to be capable of causing demyelination), *mot. for review den'd,* 100 Fed. Cl. 344 (2011), *aff'd,* 475 Fed. App'x 765 (Fed. Cir. 2012); *Whitener v. Sec'y of Health & Human Servs.,* No. 06-0411V, 2009 WL 3007380 (Fed. Cl. Spec. Mstr. Sept. 2, 2009) (meningococcal vaccine found causal of GBS); *Stewart v. Sec'y of Health & Human Servs.,* No. 06-287V, 2007 WL 1032377 (Fed. Cl. Spec. Mstr. Mar. 19, 2007) (petitioner successful in demonstrating that Hep A vaccine could cause cerebellar ataxia).

The holdings in cases involving the Hep A vaccine and demyelinating/CNS injuries reveal mostly unfavorable, factually-distinguishable precedents.[42] *Ramsey* turned in part on the fact that the petitioner could not demonstrate he had experienced the claimed injuries (unlike the present case, where Ms. Bender's TM is undisputed), although the *Ramsey* special master allowed for the plausibility of the petitioner's *Althen* prong one showing. *Ramsey*, 2011 WL 2463532, at *38 ("the evidence is at least supportive of a theory that post-vaccinal processes could lead to autoimmune encephalitis in some cases"). *Veryzer* more squarely found that the petitioner's prong one evidence was insufficient, plus treater speculation from the record in that case that the Hep A vaccine could have caused the petitioner' demyelinating injury was "undercut by the absence of objective evidence of demyelination." *Veryzer*, 2011 WL 1935813, at *21. *Stewart* - the sole disputed Hep A case resulting in favorable decision to the petitioner - is facially inapposite. It involved a disease (cerebellar ataxia) that literature and expert testimony strongly supported as associated with the wild Hep A virus, the record established onset occurred less than a week from vaccination, and molecular mimicry was the alleged mechanism for the autoimmune process (unlike here, where it has been ruled out by Petitioner's expert). *Stewart*, 2007 WL 1032377, at *2, 16, 22.

The three reasoned decisions involving the meningococcal vaccine and a demyelinating condition, by contrast, are more favorable comparables – but they too reveal facts or causal theories distinguishable from the present circumstances that limit their application herein. The most recent such case, *Giannetta*, involved the meningococcal vaccine and MS rather than TM. More importantly, the causation theory espoused in *Gianetta* involved molecular mimicry between polysaccharides in the meningococcal vaccine and structures in the CNS myelin – a mechanism that Petitioner's expert in this case has expressly disavowed. *Gianetta*, 2017 WL 4249946, at * 17.

[42] Of course, and as already noted, special masters are not literally "bound" by the prior determinations of their colleagues. *Hanlon*, 40 Fed. Cl. at 630. But it is analytically useful to consider how similar fact patterns and similar causation theories have been addressed in prior cases.

And, although the timeframe for onset (42-46 days) was comparable to what is alleged herein, Respondent's experts largely did not contest that such an onset was reasonable (unlike here – where Respondent's experts *do* contest 42 days as reasonable, and where Dr. Byers has also agreed it is longer than what she would expect to see generally). *Id.* at *24.

In *Kennedy*, the petitioner received the meningococcal vaccine and the Tdap vaccine, and experienced onset of symptoms of ADEM in 15 days, less than half the time at issue in this case. *Kennedy*, 2012 WL 1929801, at *2. Petitioner's experts also offered persuasive evidence linking the vaccines at issue to ADEM, and relied on molecular mimicry as well as the proper mechanism, with Respondent's experts failing to rebut this evidence. *Id.* at *13-14. Finally, there is *Whitener*, where a special master ruled in favor of a petitioner who claimed that she developed a peripheral neuropathic autoimmune illness, GBS, featuring aspects of TM, about a month after receiving the meningococcal vaccine. Resolution of the success of petitioner's *Althen* prong one showing in that case, moreover, turned partially on the fact that Petitioner's expert was successful in persuading the special master presiding over the case that the Government (as evidenced in a Centers for Disease Control dispatch) recognized some association between the meningococcal vaccine and GBS, thereby permitting the special master to conclude that such evidence supported petitioner's "can cause" showing. *Whitener*, 2009 WL 3007380, at *8 n.17, *20.

II. Petitioner Has Failed to Establish a Scientifically Reliable and Plausible Causation Theory

As the Court ruled in the Remand Order, I erred in finding that because Dr. Byers had forthrightly admitted that molecular mimicry was not a viable mechanism in this case, her *other* proposed mechanisms also failed. In fact, and as a re-review of her testimony and reports has clarified, Dr. Byers did *not* so intend to opine. Thus, although she did unquestionably state that molecular mimicry was not the *primary* mechanism she was proposing as part of her theory, she proposed that two other biologic mechanisms – bystander activation or epitope spreading – could instead explain the process by which the vaccines Ms. Bender received resulted in TM. She invoked a different form of molecular mimicry in connection with epitope spreading, explaining that it might involve some form of "individual" molecular mimicry specific to the injured party. Thus, and based on her assertion that cytokine production driven by vaccination could instigate an autoimmune process, these two mechanisms could explain how the vaccines could cause TM even if she could not propose molecular mimicry as a larger explanatory mechanism.

I have re-reviewed both sides' arguments with respect to these mechanisms, all of the expert reports, plus the literature offered regarding each, to determine if Petitioner did in fact meet her burden of proof on the first *Althen* prong. I find that she has not.

A. *Petitioner's Theory That Cytokine Upregulation Initiated a Pathologic Process Resulting in TM was Unreliable and Implausible*

There are several reliable and plausible components of Petitioner's theory pertaining to the role cytokines may play in autoimmune disease processes. The concept that vaccination promotes production of proinflammatory cytokines is well-known – and is often asserted by claimants in attempting to explain a vaccine's causal role in their illness. M. Sospedra, et al., *Immunology of Multiple Sclerosis,* Annual Review of Immunology, *23*(1), 683-747 (2005), filed as Ex. C, Tab 17 (ECF No. 115); *Godfrey v. Sec'y of Health & Human Servs.*, No. 10–565V, 2014 WL 3058353, at *19 (Fed. Cl. Spec. Mstr. June 11, 2014), *mot. for review granted on other grounds*, 2014 WL 7474332, (Fed. Cl. Dec. 2, 2014), *on remand,* 2015 WL 10710961 (Fed. Cl. Spec. Mstr. Oct. 27, 2015), *mot. for review den'd, slip op.* (Fed. Cl. May 25, 2016). Petitioner has also offered several items of literature that support the proposition that cytokines are involved in TM (although it is far less clear whether that role is initiatory, or secondary and/or in response to some other instigating factor like a viral infection).

But - as I have previously ruled in other cases, claimants cannot transmute scientific evidence exploring how vaccines normally function in the immune system, and/or the role cytokines play in certain ongoing disease processes like TM, into a reliable, plausible causation theory that *any* vaccine can be pathogenic simply through its transient encouragement of cytokine production, without a more specific showing that applies to the circumstances at hand – and in particular the vaccines at issue. *Olson v. Sec'y of Health & Human Servs.*, No. 13-439V, 2017 WL 3624085 (Fed. Cl. Spec. Mstr. July 14, 2017), *mot. for review den'd,* 135 Fed. Cl. 670 (2017), *appeal docketed,* No. 2018-1467 (Fed. Cir. Jan. 24, 2018). It is too far a leap from the valid science establishing what cytokines do generally, or the role they play in the disease processes that characterize TM (once it has already been initiated by infection or some other trigger), to conclude they are causal of it, based solely on these subcomponents of Petitioner's theory. *Copenhaver v. Sec'y of Health & Human Servs.,* No. 13-1002V, 2016 WL 3456436 (Fed. Cl. Spec. Mstr. May 31, 2016), *mot. for rev. den'd,* 129 Fed. Cl. 176 (Oct. 5, 2016).

Petitioner did not offer sufficient evidence – whether in the form of expert testimony or literature – to support the conclusion that the propensity of vaccines to upregulate cytokines would plausibly result in a demyelinating condition like TM. She also did not establish that cytokines like IL-6, generated at the situs of a vaccination, would invariably travel to person's CNS to cause injury there. Rather, the literature cited on this point involved direct injection of cytokines to the CNS. *See,* e.g., Kaplin; Tr. at 144, 146. Petitioner's expert testimony on this point was otherwise conclusory, and lacking in reliable support linking cytokine production in the periphery to CNS demyelinating conditions like TM. Tr. at 144, 146.

B. *Petitioner's Proposed Mechanisms Were Not Plausible or Reliable Explanations for how the Specific Vaccines in Question Could Cause TM*

As noted above, Vaccine Act petitioners are *not* required to establish a biologic mechanism. *Andreu*, 569 F.3d at 1378-79. However, petitioners frequently attempt to do so -- and not because they do not understand the nature of their evidentiary burden. Rather, mechanism is raised as an issue in cases in which more direct, primary proof – studies linking the vaccine in question to the relevant injury, or on-point Program decisions going the petitioner's way – is lacking, leading the petitioner to look for other kinds of evidence to strengthen their causation theory showing.

That is clearly the case here. Petitioner has offered no direct scientific or medical evidence (outside of case or VAERS reports) associating the relevant vaccines and TM. Accordingly, via Dr. Byers she attempted to bulwark her case in other ways, devoting a substantial amount of time at hearing to discussions of mechanisms by which *any* vaccine might cause TM – and it is therefore reasonable for me to evaluate her success on that front. *Olson*, 135 Fed. Cl. at 678-79 (no error for special master to weigh evidence supporting petitioner's proposed biologic mechanism in order to evaluate its reliability (*citing Moberly*, 592 F.3d at 1324)).

Dr. Byers's embrace of bystander activation as playing *some* role in an existing autoimmune or infectious process has medical and scientific support. But her argument that it is a plausible explanation for vaccine causation of TM was undercut greatly by Dr. Forsthuber's testimony, which established (as emphasized in articles like Murali-Krishna) that bystander activation as a concept has been demonstrated to be less reliable than previously thought. Moreover, even if Murali-Krishna can be construed (against its plain language) to support Dr. Byers's contention that some amounts of nonspecific autoreactive immune cells are still activated (even if fewer than previously understood) and can contribute to disease processes, that activation does not occur on its own. Rather, it requires an initial "insult" for the immune process to begin and then secondarily *cause* the nonspecific autoreactive T cells to respond.

Here, what would that primary insult be? Having admitted that she cannot show that the Hep A or meningococcal vaccines initiated an autoimmune process via molecular mimicry,[43] Petitioner relies on cytokine production or upregulation endemic to *all* vaccination (and thus not dependent on the formulae of the particular vaccines received) as the "spark" for the inflammatory process that in turn resulted in bystander activation. Petitioner's theory therefore was rooted (as Dr. Byers forthrightly acknowledged) in the broader proposition that virtually *any* vaccine could

[43] To do so, a petitioner will frequently attempt to demonstrate that a specific protein sequence from a component of a vaccine has some kind of sequential or structural homology with a self-structure (which in turn will explain why antibodies produced in response to the vaccine do not differentiate between the self-structure and the vaccine, resulting in an autoimmune process). *See Barone v. Sec'y of Health & Human Servs.*, No. 11-707V, 2014 WL 6834557, at *8 (Fed. Cl. Spec. Mstr. Nov. 12, 2014) (discussing various cases in which molecular mimicry was found to be a viable mechanism).

be pathogenic and result in TM. *See* Tr. at 160. But, as noted above, this component of her theory is overbroad, unsupported with evidence specific to the vaccines in question, and was not persuasively established by Dr. Byers. Accordingly, Petitioner has not established bystander activation as a plausible mechanism for how the vaccines at issue could cause TM, given both its own deficiencies as well as its reliance on cytokine upregulation as an initiatory mechanism.

Ms. Bender's showing with respect to epitope spreading was similarly lacking. Through Dr. Byers's testimony, Petitioner established that epitope spreading is a legitimate, recognized mechanism by which an autoimmune process can propagate. But Dr. Forsthuber had more demonstrated, specialized expertise on this scientific topic, and he persuasively opined that epitope spreading was a better explanation for how an autoimmune reaction would be *sustained* over time than how one would initially begin. Tr. at 303, 344. Since Petitioner admitted that the autoimmune reaction she proposed had initiated her TM could not have occurred by molecular mimicry, she again was forced to rely solely on cytokine upregulation as the "spark" that would initiate the autoimmune process exacerbated through epitope spreading (and the individualized molecular mimicry she proposed). But she did not successfully establish that vaccination *per se* would plausibly cause cytokine upregulation to the degree (or, as discussed below, length of time) necessary to constitute an initial autoimmune "hit" that could in turn trigger epitope spreading as a secondary immune response prolonging and extending the autoimmune process resulting in TM.

Overall, Petitioner successfully established that the two mechanisms proposed herein have scientific reliability on their own terms – and that, given some initial insult, they could play a role in an autoimmune process resulting in TM. But she did *not* successfully establish that the two vaccines in question could cause a demyelinating condition via these mechanisms alone, or that (absent evidence of prior infection or an autoimmune cross-reaction brought on by vaccine-induced molecular mimicry) these mechanisms could initiate a pathogenic process based solely on the immune-stimulative capacity of vaccinations generally.

C. *Petitioner's Causation Theory Had Several Other Deficiencies*

Even if I ignore these mechanism deficiencies, Petitioner's prong one showing remains inadequate for other reasons.

First, Petitioner has offered little evidence, if any, connecting the Hep A or meningococcal vaccines to her theory. The Federal Circuit has recognized that some specificity is required in establishing causation. *Broekelschen*, 618 F.3d at 1345 ("a petitioner must provide a reputable medical or scientific explanation *that pertains specifically to the petitioner's case*") (emphasis added). It is not enough to analogize the present case to what *other* vaccines can do, or to invoke broad mechanisms that could apply to *any* vaccine or immune process. *Caves*, 100 Fed. Cl. at 135 (*Althen* prong one is meaningless if petitioner can satisfy it without "empirical evidence"

connecting vaccine at issue to injury via proposed mechanism). Dr. Byers herself admitted she could not analogize her theory to evidence showing an association between the Hep B vaccine and TM (Tr. at 157) - thus eliminating from consideration those other Program decisions involving the Hep B vaccine.

Raymo provides an instructive contrast regarding what such evidence would look like. There, petitioners succeeded in demonstrating that the Tdap vaccine an 11-year old received caused her TM. They supported their causation theory not merely with two plausible mechanisms (molecular mimicry *plus* bystander activation), but also with evidence specifically demonstrating that the tetanus toxoid contained in the vaccine in question could induce a variety of "immune-mediated neurological disorders." *Raymo*, 2014 WL 1092274, at *19, *21-22.[44] In the present case, Petitioner has not offered evidence implicating any component of either specific vaccine at issue as causing TM or a comparable demyelinating condition.[45]

At best, Petitioner relied on case studies – most of which (as evidenced by Agmon-Levin) do not address the relevant vaccines at all, and which (as a class of evidence) are not typically given great weight in Program cases in any event. *Doe/16 v. Sec'y of Health & Human Servs*., No. 06–670, 2008 WL 2390064, at *14 (Fed. Cl. Spec. Mstr. June 2, 2008) (citing *Daubert*, 509 U.S. at 594–96 ("[c]ausal attribution based on case studies must be regarded with caution, largely because they lack control and thus do not provide the level of information or detail found in epidemiologic studies")).

Second, there is the Baxter epidemiologic study offered by Respondent, which directly addresses the relationship between the Hep A or meningococcal vaccines and TM – but finds no association. Although it is unquestionably the case that Vaccine Program litigants need not offer epidemiologic evidence to prevail, special masters may take note of its existence and consider it

[44] *Raymo* is also distinguishable on a more fundamental, procedural basis. There, former Chief Special Master Vowell found that she could give no evidentiary weight *at all* to Respondent's two expert opinions opposing causation. She found that one had plagiarized his opinion, while the other had significant professional licensure and disciplinary problems that the expert did not disclose or was careful to elide in his testimony. *Raymo*, 2014 WL 1092274, at *15-16. This left only the opinion of Petitioner's expert – and although Chief Special Master Vowell deemed him "not an ideal expert" given his lack of expertise in TM and long professional lapse in treating patients, his opinion was effectively unrebutted, and had enough baseline evidentiary support to meet the petitioners' burden of proof. Here, by contrast, Respondent has offered a very qualified expert whose opinion was not infected by any ethical lapses of that sort, and my decision is based on weighing the strength and persuasiveness of that opinion against Dr. Byers's opinion.

[45] Dr. Byers's brief assertions about the diphtheria conjugate contained in the meningococcal vaccine do not fill this gap. All experts agreed that this component is included to increase the vaccine's immunogenicity. But it is a large leap from that to conclude that the diphtheria component is pathogenic. Petitioner offers nothing – no expert testimony based on personal experience, and no medical or scientific literature – suggesting that the diphtheria conjugate would contribute to a disease process in this manner generally, let alone in connection with TM or the biologic mechanisms at issue. *Compare Giannetta*, 2017 WL 4249946, at *16-18 (petitioner succeeded in establishing meningococcal vaccine could cause MS, where expert linked molecular mimicry theory involving components of vaccine to argument that diphtheria conjugate could enhance cross-reaction).

when determining if a claimant has met her burden of proof. *Andreu*, 569 F.3d at 1379 (a special master may assess epidemiological evidence in "reaching an informed judgment as to whether a particular vaccination likely caused a particular injury"); *Taylor v. Sec'y of Health & Human Servs.*, 108 Fed. Cl. 807, 819–21 (Fed. Cl. 2013) (special master did not err in considering epidemiological evidence). The Federal Circuit has recently affirmed the appropriateness of considering such evidence within a special master's evidence-weighing process. *D'Toile v. Sec'y of Health & Human Servs.*, No. 2017-1982, 2018 WL 1750619, at *2 (Fed. Cir. Apr. 12, 2018) ("[n]othing in *Althen* or *Capizzano* requires the Special Master to ignore probative epidemiological evidence that undermines petitioner's theory"). Significantly, Baxter is a relatively new piece of evidence that was not available at the time other special masters considered whether any vaccine could cause TM. *See*, e.g., *Raymo*, 2014 WL 1092274, at *20 ("[t]here are no epidemiologic studies of the causes of TM, and thus no studies linking or refuting a link between the condition and vaccination").

Baxter is a scientifically-reliable, retrospective case-centered study directly involving the two vaccines at issue. It suggests there is no statistically significant association between Menactra and/or Hep A and TM – whether the timeframe is within the 30 days that all experts herein seemed to agree was reasonable for an autoimmune reaction to occur, or the longer, 42-day period at issue consistent with Petitioner's timing argument. Baxter at 1457. While I take note of Petitioner's general point that the fact that vaccine injuries are rare means that such epidemiologic evidence cannot conclusively refute a causation theory that is otherwise reliable and/or scientifically plausible, this argument does not diminish the value such evidence can have in appropriate cases. *Crutchfield v. Sec'y of Health & Human Servs.,* No. 09-0039V, 2014 WL 1665227, at *15 (Fed. Cl. Spec. Mstr. Apr. 7, 2014) ("[i]t is, in fact, *always* true that epidemiologic studies can *never* prove definitively that Factor A *never* causes Condition B . . . [b]ut it is not the Respondent's burden in this case to prove that it is *impossible* that [the relevant vaccine] can cause [the alleged injury]"). Petitioner was ineffective in rebutting Baxter, and although this article does not stand as my primary basis for finding that Petitioner did not establish a plausible causation theory, it further undermines her arguments about the causal potential of the vaccines in question.

Petitioner's reliance on VAERS data or vaccine package inserts to help establish her causal theory was also greatly misplaced. Because it is a passive reporting system, VAERS database findings that individuals have complained of a supposed adverse effect from a particular vaccine cannot be reasonably interpreted to suggest causation. For this reason, special masters do not typically afford great weight to VAERS data in determining causation – and their evaluation of the deficiencies of such evidence has been affirmed. *See Analla v. Sec'y of Health & Human Servs.,* 70 Fed. Cl. 552, 558 (2006) ("the Court [of Federal Claims] uniformly has upheld the Chief Special Master's concerns about the reliability of VAERS data") (*citations omitted*).

Similarly (and as I have previously observed in other cases), vaccine package inserts do not constitute causation evidence meriting significant weight. *Sullivan v. Sec'y of Health & Human Servs.*, No. 10-398, 2015 WL 1404957, at*20 (Fed. Cl. Spec. Mstr. Feb. 13, 2015)("[s]tatements contained in vaccine package inserts do not constitute reliable proof of causation, and cannot be deemed admissions that the vaccines in question have the capacity to harm a particular petitioner in a specific manner"); *see also Werderitsh v. Sec'y of Health & Human Servs.*, No. 99–319V, 2005 WL 3320041, at *8 (Fed. Cl. Spec. Mstr. Nov. 10, 2005) (quoting 21 C.F.R. § 600.80(l) as saying "[a] report or information submitted by a licensed manufacturer ... does not necessarily reflect a conclusion by the licensed manufacturer or FDA that the report or information constitutes an admission that the biological product caused or contributed to an adverse effect").

D. *Petitioner's Experts Were Far Less Persuasive than Respondent's*

Special masters are empowered to make credibility determinations with respect to the witnesses testifying before them - including expert witnesses. *Cedillo*, 617 F.3d at 1339. Determining the weight to give an expert's testimony has special importance when evaluating whether a Program petitioner has met her burden of proof. Given that there is *no* particular category of evidence that a claimant must offer to prevail, experts can often help fill in evidentiary holes, leveraging their experience and knowledge where no direct scientific proof exists. But to do so effectively, an expert cannot simply *declare* a theory to be reasonable or reliable and thereby satisfy a petitioner's burden of proof. Rather (and consistent with the concept that an expert's *ipse dixit* need not be automatically accepted by a special master) the opinion offered must have *some* reliable substantive grounding – whether in the expert's own professional work and experience or in the work of other scientists and medical treaters, perhaps (but not necessarily) in the form of a published, reliable item of scientific or medical literature. *Sword v. United States*, 44 Fed. Cl. 183, 188 (1999) ("[n]o judge or jury can be forced to accept or reject an expert's opinion or a party's theory at face value," and to propose that special masters must do otherwise "is to neglect the Special Master's duty to 'vigorously and diligently investigate the factual elements' underlying [a] petition") (*citing Mills v. Sec'y of Health & Human Servs.,* 27 Fed. Cl. 573, 578 (1993)).

Having re-reviewed *all* expert reports and testimony offered in this case, I can plainly state the following: Petitioner's experts were *significantly less persuasive*, and/or offered less reliable opinions, than Respondent's.

Acknowledging my error in misconstruing how molecular mimicry figured into Dr. Byers's opinion does not change this conclusion. The Court has already characterized Dr. Byers's testimony as not a "model of clarity." Remand Order at *1. At hearing, she conveyed her opinions in a haphazard, facially-contradictory manner; her confusing testimony about molecular mimicry and its relationship to her other proposed mechanisms is just one of several examples. She appeared unprepared to testify at many points. She also relied heavily on general propositions about

cytokines or mechanistic theories that were at best loosely connected to the record evidence. And she even attempted to propose the legal standard that I should apply – for example, her argument that the Program sets no limits on timeframe under the *Althen* prong three analysis – rather than simply explaining how the evidence supported her opinion.[46] Dr. Chen was in many ways worse, especially in regard to the reliability of the opinion he expressed.

Respondent's experts, by contrast, were far more persuasive. Dr. Forsthuber explained complex immunologic and scientific issues in a cogent and logical manner. He also has direct, demonstrated understanding of one of Petitioner's chosen mechanisms, epitope spreading, having written on the subject in an article *cited by Petitioner*. *See generally* Lehmann. Dr. Lotze provided a clinical physician's understanding of TM that was not matched by either of Petitioner's experts. His interpretation of the medical record (in particular, the July MRIs) as better supporting the conclusion that Petitioner's TM had to have begun very close in time to her collapse, and not weeks before as Dr. Chen proposed, was a significant component to my finding that the third *Althen* prong was not satisfied.[47] Respondent's experts provided more scientifically reliable, logical opinions that were better supported by the record and the literature they offered, and their expertise was well-matched to the questions upon which they were asked to opine.

All in all, Petitioner's showing on the first prong failed to connect proposals that had scientific validity with others that did not, or lacked links needed to knit the overall theory together. She also relied too heavily on the fact that no other explanation for her injury (e.g., the discounting of the mycoplasma infection) could be identified (Tr. at 46, 138, 373) – a consideration that the Federal Circuit in *Althen* expressly ruled out as sufficient by itself to establish a reliable causation theory. *Althen*, 418 F.3d at 1278 ("[a]lthough probative, neither a mere showing of a proximate temporal relationship between vaccination and injury, *nor a simplistic elimination of other potential causes of the injury* suffices, without more, to meet the burden of showing actual causation") (emphasis added). This was not a close case that should be resolved in Petitioner's favor.

[46] This is not the first time in which the reliability of Dr. Byers's testimony has been called into question. *See*, e.g., *Bigbee v. Sec'y of Dep't of Health & Human Servs.*, No. 06–663V, 2012 WL 1237759, at *30 (Fed. Cl. Spec. Mstr. Mar. 22, 2012) (former Chief Special Master Golkiewicz observing that "consistent with the undersigned's and my colleagues' experience with Dr. Byers as an expert, her testimony tends to be *highly generalized and missing a strong connection to the facts and medical information in the specific case*. As such, Dr. Byers' opinions tend to falter when examined by the lay person and *are exposed as unreliable when examined by a competent expert*") (emphasis added).

[47] I do not discuss Dr. Chen's testimony to the same degree herein that I review Dr. Byers's or Respondent's experts -- for the simple reason that, as discussed above, I largely found him unpersuasive as a whole.

III. Petitioner Did Not Establish the Other *Althen* Prongs with Preponderant Evidence

Even if the analysis above is (or remains) in error, Petitioner still has not met the second and third *Althen* prongs. I address them in order of their significance to my decision, rather than in their sequential order as set forth in *Althen.*

A. *Petitioner Has Not Established that her TM Began in a Medically Acceptable Timeframe*

The onset of Petitioner's TM occurred 42 days after receipt of the vaccines at issue. Such a timeframe (which even Dr. Byers admitted was long) has been deemed acceptable with respect to *other* vaccines and *different* autoimmune diseases. *See, e.g., Tompkins v. Sec'y of Health & Human Servs.*, No. 10-261V, 2013 WL 3498652, at *33 (Fed. Cl. Spec. Mstr. June 21, 2013) (discussing evidentiary support for onset of GBS occurring up to 42 days post-vaccination), *mot. for review den'd*, 117 Fed. Cl. 713 (2014). But *most* cases involving claims of vaccine-induced TM (in keeping with its acute nature) resulting in a successful entitlement decision involve a far shorter timeframe. *See, e.g., Raymo*, 2014 WL 1092274, at *23 (onset of TM three to four days after receipt of Tdap vaccine); *Moore v. Sec'y of Health & Human Servs.*, No. 07-0645V, 2010 WL 5113199 (Fed. Cl. Spec. Mstr. Aug. 31, 2010) (onset of TM 24 hours after receipt of influenza vaccine); *Schmidt*, 2009 WL 5196169 (onset of TM 27 days after receiving influenza vaccine). And I am not otherwise compelled to accept timeframes relating to vaccines other than those at issue herein in determining what would be a medically acceptable timeframe in this case. *See M.S.B. v. Sec'y of Health & Human Servs.*, 117 Fed. Cl. 104, 130 (Fed. Cl. 2014) ("[a] decision, based on a different factual record, that it was arbitrary to require that symptoms manifest within [a specific time period], hardly shows that the decision under review was reached in an arbitrary manner" when the case under review concerned different vaccines). Accordingly, it behooved Petitioner to support her contentions relating to *Althen* prong three by referencing persuasive evidence involving the Hep A or meningococcal vaccines.

Petitioner's evidence supporting the medical acceptability of the 42-day period came largely from Dr. Byers, who in turn relied on some case study-oriented literature (primarily Agmon-Levin), some individual case studies, and her own opinions based on her individual expertise. With respect to primary literature, however, Dr. Forsthuber persuasively established that Agmon-Levin (which does not address either of the two vaccines at issue) was simply a collection of individual case reports that careful scrutiny revealed proved far less than contended, and thus lacked sufficient medical reliability to support Ms. Bender's timeframe assertions. Tr. at 254. I have in other cases noted that Agmon-Levin does not establish medically acceptable timeframes for autoimmune conditions when (as here) applied to vaccines or injuries the article does not discuss. *See, e.g., Garner,* 2017 WL 1713184, at *16. Thus, although Agmon-Levin directly addresses TM, the disparate nature of the case studies it relies on, along with the fact that it does not mention the vaccines relevant herein, greatly reduces its evidentiary weight.

The individual case studies cited by Dr. Byers or Dr. Chen were also similarly unpersuasive in supporting the timeframe at issue. The Kerr article itself recognizes something well understood in the Vaccine Program (and observed above): case studies are *not* robust evidence of causation. Kerr at 341; *Holt v. Sec'y of Health & Human Servs.*, No. 05-0136V, 2015 WL 4381588, at *28 (Fed. Cl. Spec. Mstr. June 24, 2015) (discussing evidentiary limitations of case study evidence in establishing vaccine causation). And – like the TM case law already mentioned - most of those offered by Petitioner involved dramatically *shorter* timeframes for onset in any event. *See, e.g.*, R. Riel-Romero, *Acute Transverse Myelitis in a 7-month-old Boy after Diphtheria-Tetanus-Pertussis Immunization,* 44 Spinal Cord 688-91 (2006), filed as Ex. 35 (ECF No. 109) (symptoms onset 17 days after vaccination); E. Whittle, et al., *Transverse Myelitis After Diphtheria, Tetanus, and Polio Immunization,* 4 Brit. Med. J. 1450 (1977), filed as Ex. 36 (ECF No. 109) (onset six to seven days after vaccine administration). Shorter onsets are wholly consistent with the recognized acute nature of TM – and also with Dr. Byers's own admissions about the timeframe she would expect to see in most cases. Byers Rep. at 7; Tr. at 77, 79.

Dr. Byers's pronouncements on the subject of timeframe proved even less persuasive than the case study evidence. She had no individualized expertise with TM, and therefore could not cite her own experience on the subject. Rather, she offered a particularly expansive reading of Vaccine Program precedent, proclaiming that as a matter of law there is no formal "limit" to the amount of time that can pass from vaccination to injury. *See, e.g.*, Tr. at 102-03, 149. Putting aside the fact that Dr. Byers's role as an expert does not extend to opining on the proper application of legal standards in this case, her assertions misstate the law. Even if controlling precedent does not prohibit non-Table claims based solely on the relevant onset timeframe, the *entire purpose* of the timeframe causation prong is to gauge whether the amount of time that has passed from vaccination to injury in a particular case is (from a legal standpoint) medically acceptable given the circumstances. Implicit to this is the reasoned view that in any case, *some* amount of time will be too long, even for vaccines that have been established as causal of particular illnesses or injuries. Were this not so, *Althen* prong three would be toothless. *See, e.g., Hennessey v. Dep't of Health & Human Servs.*, 91 Fed. Cl. 126, 142 (2010) (rejecting causation theory that "any conceivable timing could qualify as an appropriate temporal relationship" as rendering "*Althen's* third prong a nullity").

Petitioner's timeframe arguments also are unsupported by her *Althen* prong one causation showing. Petitioner's theory (accepting it as plausible for sake of argument) is that vaccine-induced cytokine upregulation can initiate a pathologic process (whether via bystander activation or epitope spreading) resulting in TM. But she has offered no reliable support, in the form of expert testimony or filed medical literature, establishing that any vaccine could instigate the chronic production of cytokines for a long enough period of time, sufficient in severity and degree, to cause an acutely-presenting autoimmune condition like TM via the proposed mechanisms. It has not

been demonstrated herein that vaccine-induced cytokine production is more than a transient process that is localized to the site of vaccine administration. *Godfrey*, 2015 WL 10710961; *Koehn*, 773 F.3d at 1244. Nor did Dr. Byers offer reliable proof that her preferred biologic mechanisms could (and in the absence of an initial instigating factor, like direct infection) occur 42 days-post vaccination.

Finally, the actual medical record in this case does not corroborate Petitioner's timeframe argument. Petitioner admits there is no record evidence of any clinical symptoms of TM between her vaccinations and July 10, 2009 – when she first presented to medical treaters. Petitioner can also point to no testing results or other persuasive evidence from her initial hospitalization that would circumstantially bulwark the suggestion (largely advanced in Dr. Chen's testimony) that a subclinical autoimmune process was underway *before* July 10th, thus supporting the inference of an earlier onset more consistent with what Drs. Byers and Forsthuber agreed was most likely in the majority of TM cases.

Respondent, by contrast, established the contrary. Dr. Lotze - a highly qualified pediatric neurologist – emphasized, in a comparison of the July 2009 MRIs performed four days apart, that Petitioner had in his view experienced a rapid, progressive escalation of her lesions shortly after her collapse. Lotze Rep. at 3. Thus, the autoimmune process at issue more likely than not began close in time to that collapse – not weeks before. This reading of the evidence is consistent with TM's acute nature, and bulwarks the conclusion that whatever actually caused Ms. Bender's TM more likely than not occurred well *after* her vaccinations seven weeks before. Petitioner did not otherwise offer literature or other evidence supporting Dr. Chen's contention that TM would invariably be characterized by a subclinical onset that would predate obvious symptoms.

B. *The Record Does Not Support the Conclusion that the Hep A or Meningococcal Vaccines Did Cause Petitioner's TM*

Petitioner has successfully established that the IgM levels relied upon by initial treaters as pointing to a mycoplasma infection as the cause of her TM were a false positive. Moreover, other than elevated white blood cell/lymphocyte levels observed by Respondent's experts as possibly suggesting an infectious process was at work, the record contains no other clues as to alternative causes for her condition. From this, Petitioner argues, the "only" remaining conclusion is that her TM was vaccine-caused. *See, e.g.*, Tr. at 46, 138, 373. However, it is virtually black-letter law in the Vaccine Program that evidence of the development of a disease temporally following a vaccination is insufficient on its own to establish causation. *Althen*, 418 F.3d at 1278; *Grant*, 956 F.2d at 1148-49. Rather, corroborative record proof demonstrating the "logical sequence of cause and effect" is required.

As noted above, a wide variety of indirect and circumstantial evidence can be offered to support *Althen* prong two, whether in the form of test results, record evidence of symptoms, or

witness testimony as to an injured party's state at the relevant time. Such evidence is lacking in this case. Petitioner cannot point to anything in the 42-day period prior to her first symptom that would suggest that a vaccine-caused autoimmune and inflammatory process was in fact under way. She also cannot identify record evidence from the time of her initial treatment that would give circumstantial support to her theory. No medical test results shed light on the matter (besides confirming her TM).

In addition, the record does not establish that any treaters ever implicated the Hep A or meningococcal vaccines as causal of Petitioner's TM (although the existence of the vaccinations was made known at the outset of her treatment). *See, e.g.,* Ex. 15 at 79, 89. It is no response for Petitioner to point out that treaters appear, at first, to have mistakenly concluded that she had a prior mycoplasma infection that might explain the source of her TM, and were therefore incurious about other etiologies for Petitioner's symptoms. Later-in-time treaters (in particular, TM specialist Dr. Kerr) did not display that bias in their attempt to pinpoint the etiology of Petitioner's disease – and they did not propose the vaccines could be causal.

I also do not find persuasive Petitioner's conclusory suggestions that she was likely idiosyncratically "susceptible" to an autoimmune attack, thereby rendering the expected immunogenicity of the meningococcal and Hep A vaccines toxic for her. Petitioner did not establish any proof of such susceptibility. It is otherwise circular reasoning to propose that because vaccine injuries are rare, and because a claimant allegedly experienced a rare, post-vaccination injury, that the individual must have somehow been susceptible even if the nature of that susceptibility has not been identified or demonstrated. *See T.M. v. Sec'y of Health & Human Servs.*, No. 08-284V, 2016 WL 11087157, at *24 (Fed. Cl. Spec. Mstr. Aug. 9, 2016), *mot. for review den'd,* 133 Fed. Cl. 78 (2017). Even the relaxed evidentiary standards of the Vaccine Program require more than such speculative reasoning, and yet that appears to be the basis for much of Dr. Byers's opinion. *See, e.g.*, Tr. at 76.

My analysis of the sufficiency of Petitioner's prong two showing is also informed by the wholly unpersuasive quality of Dr. Chen's opinion and testimony. Dr. Chen's explanation of the medical records had some utility - especially in his arguments about timeframe, which were reasonable (even if effectively rebutted by Dr. Lotze's counter-reading of the July 2009 MRIs). But I otherwise did not find his testimony (which was conclusory and presented in a confusing manner) helpful to Petitioner in establishing her burden of proof. Dr. Chen also advanced opinions about matters not presently before me that diminished his credibility – for example, the wholly-discredited concept in the Vaccine Program that vaccines cause autism. *See, e.g.*, Chen Rep. at 8-9; Tr. at 225-28. Although my misgivings about the persuasive character of Dr. Chen's opinion are somewhat tertiary to my previously-discussed review of the substantive merits of Petitioner's claim, they nevertheless are reasonably factored into my ultimate determination. *Porter*, 663 F.3d at 1250.

IV. Other Considerations on Remand

The Remand Order directs me to "clearly articulate how the medical literature and absence of test results" informed my determination. Remand Order at *1 n.3. Although I have attempted to address these matters above in the context of my redetermination of entitlement, I will briefly revisit both points herein in summary.

First, I have found that Petitioner *did* offer supportive and reliable literature for certain elements of her causation theory. As noted, some of the literature (bulwarked by Dr. Byers's testimony) reliably established that cytokines are involved in the process of TM, what roles they perform, and how all vaccines can (transiently) encourage their production. But there is an absence of the same kind of reliable, independent support establishing that (a) cytokines can be sufficiently pathogenic to instigate an autoimmune process, (b) they can directly cause TM (as opposed to be involved in its processes once initiated), and (c) that vaccination in the periphery resulting in cytokine upregulation could *alone* cause pathologic processes mediated by cytokines in the CNS. And Dr. Byers's testimony was too conclusory, or unreliable given her lack of direct expertise studying such issues, to bridge evidentiary gaps. Noting this to be the case is not "requiring" literature – it is weighing the evidence offered.

Petitioner also has not rebutted Baxter – a recent, reliable piece of literature that undercuts her arguments associating TM with the two vaccines directly at issue. My giving weight to Baxter is *not* equivalent to obligating Petitioner to offer her own epidemiologic evidence. Rather, and consistent with Federal Circuit precedent, I am *considering* it, finding it reliable, and noting that it has not been rebutted. Petitioner has also not offered reliable proof that would establish the 42-day period of onset is medically acceptable. She relied heavily on Agmon-Levin, but even if that article provides medically-reliable evidence on the timeframe of many cases of vaccine-caused TM, it does not address the vaccines in question and involves many factually-distinguishable situations, reducing its evidentiary weight.

Second, I have noted above that Petitioner cannot point to medical record evidence for the period between her vaccinations and onset to corroborate her theory that she was at that time undergoing an autoimmune inflammatory process. Petitioner's argument in response (as implied by her motion for review) seems to be that it was unreasonable to hold that lack of evidence against her – either because testing relevant to certain components of her theory (like vaccine-induced cytokine upregulation) is not commonly performed, or because the initial, mistaken view of treaters that a mycoplasma infection was the cause of her TM dissuaded them from looking for other possible explanations.

Admittedly, these are fair inferences that could be drawn from this record. However, that same record (as Respondent established) strongly suggests (given the progression of lesions evident from the July 2009 MRIs) that Petitioner's TM began close in time to her clinical manifestation of symptoms, not before – widening the gap between the vaccinations and onset. And no treaters – either at the time of Petitioner's initial presentation in July 2009 or later – ever proposed the vaccines she had received were causal of her TM. I give such facts greater weight than Petitioner's explanations for why certain testing evidence might be absent from the record. Accordingly, I have found that the absence of indicia of inflammation, symptoms, or other evidence that some autoimmune process had begun before July 10th is less likely attributable to treaters identifying the wrong cause for her TM, and more supportive of the conclusion that the process resulting in her TM began close in time to her presenting symptoms and not before – reducing the likelihood that the vaccines were the initiatory factors in the process.

The lack of evidence corroborating that an autoimmune process is underway, or that the theory proposed did more likely than not occur, is reasonable to consider when weighing if a claimant has met the "did cause" burden. *See Cozart v. Sec'y of Health & Human Servs.*, No. 00-590V, 2015 WL 6746616, at *17-18 (Fed. Cl. Spec. Mstr. Oct. 15, 2015) (petitioners failed their burden under *Althen* Prong Two when they provided no evidence to support their theory that a decedent's vaccinations acted as an extrinsic stressor, nor did they provide any evidence to support their position that the peripheral cytokines released in response to the vaccines actually did communicate with the central nervous system in the way provided by their theory of causation), *mot. for review den'd,* 126 Fed. Cl. 288 (Fed. Cl. 2016); *see also Bigbee v. Sec'y of Health & Human Servs.*, No. 06-663V, 2012 WL 1237759, at *38 (Fed. Cl. Spec. Mstr. Mar. 23, 2012) (even if petitioners' theory had satisfied *Althen* Prong One, the complete lack of preponderant evidence of infection, consistent with that theory, failed to satisfy *Althen* Prong Two). Without some preponderant proof to support Petitioner's "can cause" theory, it does not matter how scientifically plausible the theory may be.

V. Petitioner Did Not Meet Her Overall Burden of Proof

It is indisputable that claimants have an *overall* burden of proof based on a preponderance standard. *W.C.*, 704 F.3d at 1356; *Tarsell*, 133 Fed. Cl. at 793. As a result, a Vaccine Program claim may fail even if one or two of the three *Althen* prongs have been satisfied. *See Gramza v. Sec'y of Health & Human Servs.*, No. 15-247V, 2018 WL 1581674 (Fed. Cl. Spec. Mstr. Feb. 5, 2018), *appeal docketed* (Fed. Cl. March 7, 2018) (finding that even though Petitioner established *Althen* prong one, by failing to establish the other two prongs she failed to meet her overall burden of proof); *Auch v. Sec'y of Health & Human Servs.*, No. 12-673V, 2017 WL 1034396 (Fed. Cl. Spec. Mstr. Jan. 13, 2017) (same).

This case presents an apt example of a claim that lacks overall preponderant support. Petitioner's claim comes down to this: the vaccines she received (like *any* vaccine administered in the United States) have the capability of causing a pro-inflammatory "cytokine storm" that can lead to an autoimmune disease such as TM, via certain biologic mechanisms that can apply even in the absence of direct infection or molecular mimicry. Susceptible individuals are more likely to experience the rare side-effect of such an autoimmune injury. Because we know that Petitioner received two vaccines, and then 42 days later (a period that Dr. Byers admits is on the outermost end for manifestation of an autoimmune reaction) developed TM, it is more likely than not that she is just such a person – especially in the absence of an alternative explanation for the cause.

Although I have found that Petitioner's causation theory is not reliable, my determination on the plausibility of Petitioner's theory could still be incorrect. But even so – establishing a plausible causation theory alone *is not sufficient grounds alone to prevail in the Vaccine Program*, as the Federal Circuit makes clear. *See Grant*, 956 F.2d at 1148. The overall claim must have preponderant *evidentiary* support. Here, the claim does not. The record does not support the conclusion that the Hep A and meningococcal vaccines "did cause" Petitioner's TM in the manner proposed. Moreover, the timing of onset is too long, and there is no persuasive record evidence, expert testimony, or medical literature that would explain the 42-day gap (especially in light of Petitioner's inability to connect the Hep A or meningococcal vaccines to TM).

What is left, then, is the onset of Petitioner's TM 42 days after her vaccinations. Dr. Byers was fairly clear in explaining that because there was an absence of *other* potential explanations, she favored vaccine causation – precisely on the grounds of the temporal relationship. Tr. at 46, 138, 373. This does not constitute a successful preponderant evidentiary showing. *Caves*, 100 Fed. Cl. at 135.

CONCLUSION

Ms. Bender and her family are brave people who have acted valiantly in the face of a debilitating illness, and are to be commended in their unstinting efforts to ensure Petitioner receives good care and lives as whole a life as possible. My sympathies for their suffering, and appreciation for their diligence in pursuing this claim, make it difficult to resist awarding them damages. But I would be remiss in carrying out my duties if I ruled in their favor for such reasons, given the insufficient record supporting Petitioner's claim. Accordingly, based upon the aforementioned analysis, I conclude that Ms. Bender has not carried her burden of proof, and therefore I must DENY entitlement in this case.

In the absence of a timely-filed motion for review (see Appendix B to the Rules of the Court), the Clerk shall enter judgment in accord with this decision.[48]

IT IS SO ORDERED.

/s/ Brian H. Corcoran
Brian H. Corcoran
Special Master

[48] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment by filing a joint notice renouncing their right to seek review.